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CHRONIC BARBITURATE INTOXICATION

An Experimental Study

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IN RECENT years abuse of barbiturates has become a problem of increasing concern to physicians, various lay groups, law enforcement officers and legislators. The production of barbiturates has steadily increased and now appears to exceed greatly the amount needed for therapeutic purposes.[1] In 1948 the total production of barbiturates in the United States was 672,000 pounds (336,000 Kg.), an amount roughly equivalent to 3,057,730,000 capsules or tablets of 0.1 Gm. each, or approximately 24 doses for each person in the United States. Acute intoxication with barbiturates accounts for about 25 per cent of all patients with acute poisoning admitted to general hospitals[2]; and more deaths are caused by barbiturates, either accidentally ingested or taken with suicidal intent, than by any other poison.[3] Various articles in the lay press[4] have attributed automobile accidents and various crimes to

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1. United States Tariff Commission: Synthetic Organic Chemicals Production and Sales, Washington, D. C., United States Government Printing Office, 1948.

2. Goldstein, S. W.: Barbiturates: A Blessing and a Menace, J. Am. Pharm. A. (Scient. Ed.) **36**:5 (Jan.) 1947. Rubitsky, H. J., and Myerson, R. M.: Acute Phosphorous Poisoning, Arch. Int. Med. **83**:164 (Feb.) 1949.

3. Barbiturates Leading Cause of Fatal Accidental Poisoning, Statist. Bull. Metrop. Life Insur. Co. **29**:7 (Aug.) 1948. Accident Fatalities in the United States, 1946, Vital Statistics Special Reports, National Summaries, Federal Security Agency, United States Public Health Service, National Office of Vital Statistics, vol. 29, no. 15, 1949. Trichter, J. C.: Control over the Distribution of Barbiturates and Their Public Health Importance, J. Quart. Bull. A., Food and Drug Officials **9**:127, 1946.

4. Carlisle, N., and Carlisle, M.: Thrill Pills Can Ruin You, Collier's **123**:20 (April 23) 1949. Werble, W.: Waco Was a Barbiturate Hotspot, Hygeia **23**:432 (June) 1945. Stone, W. J.: 1,250,000,000 Doses a Year, ibid. **20**:662 (Sept.) 1942.

barbiturate intoxication and have also stated that illegal trafficking in barbiturates is being carried on by unscrupulous pharmacists and by drug peddlers or "goof ball" salesmen. The seriousness of the situation is reflected by the large number of states which have passed laws regulating the sale of barbiturates [5] and by the continuing agitation for Federal control of barbiturates.

Practically all the lay articles and most of the medical articles which have appeared in the American literature have been concerned with acute barbiturate poisoning, and only a relatively small number of articles have dealt with chronic barbiturate intoxication.[6] In general, the latter agree that the signs and symptoms of chronic barbiturate intoxication include somnolence; confusion; ataxia in gait and station; nystagmus; dysarthria; dyssynergia; hyperreflexia; adiadokokinesis; coarse tremors of tongue, lips and fingers; increased emotional instability, and occasionally a psychosis characterized by disorientation and unorganized delusions of paranoid type. Although these articles do not mention the appearance of signs of abstinence on withdrawal of barbiturates, some of the authors [7] have termed the condition barbiturate "addiction."

A large number of papers [8] and one monograph [9] dealing with chronic barbiturate intoxication and with withdrawal of barbiturates

5. Fischelis, R. P.: A Review of the Present Status of Barbiturate Regulation, J. Am. Pharm. A. **35**:193 (July) 1946.

6. (*a*) Curran, F. J.: The Symptoms and Treatment of Barbiturate Intoxication and Psychosis, Am. J. Psychiat. **95**:73 (July) 1938; (*b*) Current Views on Neuropsychiatric Effects of Barbiturates and Bromides, J. Nerv. & Ment. Dis. **100**:142, 1944. (*c*) Work, P.: Barbital (Veronal) Addiction, Arch. Neurol. & Psychiat. **19**:324 (Feb.) 1928. (*d*) Sands, I. J.: Barbital (Veronal) Intoxication, J. A. M. A. **81**:1519 (Nov. 3) 1923. (*e*) Ashworth, N. C.: Injurious Effect of Veronal and Related Drugs and Suggestion for More Restricted Use, South. M. J. **22**:813 (Sept.) 1929. (*f*) Robinson, G. W.: Addiction to Barbituric Acid Derivatives, J. Missouri M. A. **34**:374 (Oct.) 1937; (*g*) Observations on Addiction to Barbituric Acid Derivatives, ibid. **36**:490 (Dec.) 1939. (*h*) Wagner, C. P.: Barbiturate Addiction: A Report of the Study Made by the Society's Committee on Drug Addiction, Connecticut M. J. **6**:124 (Feb.) 1942. (*i*) Stone, C. W.: Some Undesirable Effects from the Prolonged Use of Barbiturates, Ohio State M. J. **32**:209 (March) 1936. (*j*) Ashworth, W. C.: The Injurious Effects of Veronal and Related Drugs and a Suggestion for Their More Restricted Use, South. Med. & Surg. **98**:592 (Nov.) 1936. (*k*) Moersch, F. P.: The Abuse of Sedative Drugs in the Practice of Medicine, M. Clin. North America **30**:879 (July) 1946.

7. Work.[6c] Sands.[6d] Robinson.[6f, g] Wagner.[6h]

8. (*a*) von Muralt, L.: Ein Fall von akuter Psychose bei chronischer Trional-Veronal-Vergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **22**:122, 1914. (*b*) Schneider, K.: Ein Veronaldelirium, Gerichtl. Med. **72**:87, 1915. (*c*) Pohlisch, K.: Ueber psychische Reaktionsformen bei Arzneimittelvergiftungen, Monatsschr. f. Psychiat. u. Neurol. **69**:351, 1928. (*d*) Schubert, H.: Zur Frage des Schlafmit-

have appeared in the German literature. All these articles agree that abrupt withdrawal of barbiturates from chronically intoxicated persons may be followed by the development of convulsions or a psychosis or both. The German authors have all been impressed with the resemblance of the disturbance following withdrawal of barbiturates to alcoholic delirium tremens. It is strange, in view of the remarkably clear descriptions of the barbiturate withdrawal syndrome by these German writers, that the condition should so long have escaped notice in the United States. Since 1940, however, the occurrence of convulsions following withdrawal of barbiturates has been described in a number of articles in the American literature,[10] but the development of a psychosis, although mentioned by Stone [9i] and by Osgood [10d] has received little attention.

Since 1941 an increasing number of persons with addiction to morphine who were also taking large amounts of barbiturates (usually pentobarbital, secobarbital [seconal® sodium; sodium 5-allyl-5-(1-methylbutylbarbiturate)] or amobarbital sodium [amytal® sodium; sodium isoamylethylbarbiturate]) have been admitted to the United States Public Health Service Hospital at Lexington, Ky. In many instances, if barbiturates were abruptly withdrawn from these patients, or if the dose of barbiturates was suddenly reduced to 50 per cent or less of the amount the patient was accustomed to taking, convulsions and/or a psychosis occurred. Even though this clinical experience was in agreement with that reported in the literature, it was impossible from the clinical data to determine whether or not the phenomena observed were actually due to the withdrawal of barbiturates. The histories of

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telmissbrauches, Med. Welt **11**:47 (Jan. 9) 1937. (*e*) von Büssow, H.: Beobachtungen an einem Phanodormdelir, Nervenarzt **8**:362, 1935. (*f*) Dörries, H., and Langelüddeke, A.: Weitere Beobachtungen über Phanodormpsychosen und Phanodormsucht, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:658, 1936. (*g*) Busche, K. H.: Phanodormsucht mit psychischen Störungen, Inaug. Dissert., Erlangen, K. Dörres, 1937. (*h*) Meerloo, A. M.: Slaapmiddelzucht en slaapmiddelvergiftiging, Nederl. tijdschr. v. geneesk. **81**:668 (Feb. 13) 1937. (*i*) Schmidt, G.: Erscheinungen bei Luminalentzug, München. med. Wchnschr. **85**:1944 (Dec. 16) 1938. (*j*) Meyer, H. J.: Ueber chronischen Schlafmittelmissbrauch und Phanodormpsychosen, Psychiat-neurol. Wchnschr. **41**:275 (June 17) 1939. (*k*) Raithel, W.: Beobachtungen bei plötzlichem Luminalentzug, ibid. **41**:484, 1939.

9. Pohlisch, K., and Panse, F.: Schlafmittelmissbrauch, Leipzig, Georg Thieme, 1934.

10. (*a*) Dunning, H. S.: Convulsions Following Withdrawal of Sedative Medication, Internat. Clin. **3**:254, 1940. (*b*) Kalinowsky, L. B.: Convulsions in Non-epileptic Patients on Withdrawal of Barbiturates, Alcohol and Other Drugs, Arch. Neurol. & Psychiat. **48**:946 (Dec.) 1942. (*c*) Brownstein, S. R., and Pacella, B. L.: Convulsions Following Abrupt Withdrawal of Barbiturate: Clinical and Electroencephalographic Studies, Psychiatric Quart. **2**:112 (Jan.) 1943. (*d*) Osgood, C. W.: Convulsive Seizures Following Barbiturate Withdrawal, J. A. M. A. **133**:104 (Jan. 11) 1947.

these patients are unreliable with respect to dose because of deliberate exaggeration of the amount taken, as well as the patient's inability to recall the amount used on account of the drunkenness and confusion produced by the drug. Since all the cases represented a mixed addiction to morphine and barbiturates, and frequently to alcohol and other drugs as well, the possibility that the convulsions and psychoses were due to poisoning or to the withdrawal of a combination of drugs could not be excluded. Most of the patients were emaciated and malnourished, so that it seemed possible that malnutrition might play a role in the genesis of symptoms. The majority of the patients received some barbiturates, and withdrawal of morphine was carried on simultaneously with that of the barbiturates, so that it was impossible to separate symptoms and changes in behavior due to abstinence from barbiturates from those due due to abstinence from morphine. Since the physical and mental state of the patient prior to chronic intoxication with barbiturates was unknown, it was difficult to determine whether the development of convulsions and psychoses was dependent on an underlying psychotic or epileptic diathesis or whether any permanent physical and mental state of the patient prior to chronic intoxication These difficulties in interpreting the clinical data apply to the cases reported in the literature, as well as to the cases studied at Lexington.

In order to obtain information concerning the points raised in the preceding paragraph, large amounts of barbiturates were administered for extended periods to volunteers under carefully controlled conditions and then abruptly withdrawn.

EXPERIMENTAL INVESTIGATION

Subjects.—Five men with former addiction to morphine, who were serving sentences for violations of the Harrison Narcotic Act, volunteered to undergo the experiment. They had been completely abstinent from morphine and other drugs for at least three months prior to the experiment. They had no significant physical defects, and all had normal electroencephalograms. They had all served more than one sentence for violation of the Narcotic Act and had long records of alcoholism, delinquency, vagrancy or antisocial acts. In the past, each had had a psychiatric examination at least once and his condition had been diagnosed as a character disorder (constitutional psychopathic inferiority). These diagnoses were confirmed by other psychiatric examinations before the subjects were accepted for the experiment.

S 1,[11] a white man aged 42, became alcoholic at the age of 22. He had had one attack of delirium tremens, after a prolonged debauch, in 1932. He began the use of morphine for the relief of symptoms following bouts of alcoholism in 1938 and

11. The persons serving as subjects for the experiment are designated by a number. The letter preceding the number indicates the drug the subject was taking, i. e., S for secobarbital, P for pentobarbital and A for amobarbital.

since that time had been treated for addiction to narcotics thirteen times. Since 1946 he had used 0.8 to 1.5 Gm. of pentobarbital daily, in addition to morphine, whenever he was not in an institution. In 1948 he had one convulsion after he had completely abstained from pentobarbital for forty-eight hours. He had never had any other convulsions, and there was no history of epilepsy in his family. No evidence of psychosis was elicited during the psychiatric interview. His Rorschach examination indicated a constricted person with a good grasp of reality, inability to respond affectively to external stimuli and poverty of intellectual function. On the basis of the results of the psychiatric interview and the Rorschach examination, the diagnosis of a character disorder with some anxiety, inadequacy and dependency was made.

S 2, a white man aged 42, had received several sentences for burglary and for violations of the Narcotic Act. He had used morphine or similar drugs since the age of 18 and had been treated for addiction twelve times. He had never abused alcohol and had taken barbiturates only occasionally. There was no evidence of psychosis and no familial or personal history of epilepsy. The results of his Rorschach examination were consistent with a rigid, extremely constricted person who had a good grasp of reality and little capacity for response to emotional stimuli. The diagnostic impression was that of a character disorder with compulsive features.

P 3, a white man aged 40, had been addicted to morphine fifteen times. He had drunk to excess prior to becoming addicted to morphine but had used barbiturates only occasionally. There was no evidence of psychosis and no history of epilepsy. His Rorschach examination indicated evasiveness, with a great deal of responsiveness to affective stimuli, inability to think analytically and depressive trends. The diagnostic impression was that of a character disorder with dependency, inadequacy and depressive tendencies.

P 4, a white man aged 48, had led a wandering, vagrant life since the age of 16. He became addicted to morphine at the age of 18, abused alcohol at times but seldom took any barbiturates. His intelligence was low normal (quotient, 81). There was no evidence of psychosis and no personal or familial history of epilepsy. He had been married and divorced three times. His Rorschach examination indicated a constricted person with sparse fantasy life, little affective responsiveness, passivity and a strong grasp of reality. The diagnostic impression was that of a character disorder with inadequacy.

A 5 was a handsome white man aged 30. His father was alcoholic and abused the patient, as well as his mother and sisters. The patient's mother and father were divorced when he was 17 years of age. Shortly thereafter he was sentenced to six months in a reformatory for seducing a young girl. In the reformatory, he heard about barbiturates and, after discharge, began to take them with alcohol. He had had abrupt withdrawal of barbiturates several times after arrests for being drunk but stated that he did not remember what happened during the withdrawals. He began to use morphine when he was 21 years of age and had been addicted to this drug three times. The patient was always quiet and withdrawn and associated very little with other patients. No evidence of psychosis and no personal or familial history of epilepsy was elicited during psychiatric interviews. His Rorschach examination indicated a self-punitive person, who retreated into fantasy instead of reacting affectively to the external environment. The diagnostic impression was that of a character disorder with schizoid traits.

General Conditions.—The patients were housed in a special ward devoted to clinical investigation and were separated almost completely from contact with other patients in the institution. All drugs were administered orally in the form of 0.1 Gm. capsules or tablets. Two subjects received secobarbital sodium; 2, pentobarbital sodium, and 1, amobarbital sodium. Great precautions were taken to prevent introduction of drugs, other than those prescribed, into the experimental environment. The patients were constantly observed by trained attendants.

Periods.—The experiment was divided into five periods: (1) Preliminary. During this period, physical, psychologic, neurologic and psychiatric examinations were completed, roentgenograms of the chest and skull were obtained, the effects of single doses of the various barbiturates were determined and all preliminary observations were completed. This period lasted fourteen to twenty-one days. (2) Chronic administration. During this period the patients received large amounts of barbiturates daily. The drugs used, the total amounts taken, the total number of days and the dosage schedule are summarized in table 1. (3) Period of withdrawal. Withdrawal of barbiturates was abrupt and complete in all instances. One patient had to be returned to secobarbital on the ninth day of withdrawal, for reasons which will be discussed later. The period of withdrawal covered twelve to thirteen days in the remaining four instances. (4) Recovery. During this period patients no longer resided in the experimental ward but lived in the dormitories. They returned at appropriate intervals for physical, psychologic, psychiatric and neurologic examinations. This period was two months or more in length. (5) Reintoxication. After the period of recovery was completed, 4 of the patients were abruptly placed on the same dosage of barbiturates they were receiving when withdrawal began. This period lasted only two or three days.

Observations.—The following clinical observations were made three times daily after ten minutes of bed rest: rectal temperature, pulse rate, respiratory rate and blood pressure. The body weight, caloric intake (calculated from tables of food values) and number of hours of sleep were recorded once daily. Once a week the temperature, pulse rate, respiratory rate, blood pressure and respiratory minute volume (obtained with a standard basal metabolism apparatus with bell filled with oxygen) were determined before and every thirty minutes for five hours after the 9 a.m. dose.

The following neurologic examinations were made once a week during the period of chronic administration of the drug: tests for the patellar, achilles, biceps, triceps deep reflexes, the superficial abdominal and cremasteric reflexes, the Babinski reflex, and the ankle clonus; tests for ataxia in gait and station; finger to nose tests; determination of pupillary reactions; tests for nystagmus; tests for dysarthria, and observations for tremor of the extended hands and fingers. These tests were performed before and every thirty minutes for five hours after the 9 a.m. dose.

The following laboratory examinations were made twice during the preliminary period, once every two weeks during the period of chronic administration and at appropriate intervals during the period of withdrawal: urinalysis; total red, white and differential blood cell counts; hemoglobin determinations; nonprotein nitrogens estimations, thymol turbidity and cephalin flocculation tests, and serum bilirubin determination. Fasting blood sugars were determined four times during the preliminary period, once every two weeks during the period of chronic administration, daily during the first three days of withdrawal and once every third day during the remainder of the period of withdrawal.

The total, true and pseudocholinesterase contents of the serum were obtained twice during the preliminary period, once a week during the period of chronic administration and during the second and seventh days of withdrawal. The total cholinesterase content was determined according to the method of Ammon,[12] using acetylcholine bromide as the substrate. Pseudocholinesterase was determined by the method of Mendel, Hawkins and Nishikawara,[13] using benzoylcholine chloride as substrate. The value for true cholinesterase was obtained by subtracting the value for pseudocholinesterase from that for total cholinesterase.

Electroencephalograms, recorded by the technic described by Isbell and associates,[14] were obtained several times before and at intervals after single doses of barbiturates during the preliminary period. In the period of chronic administration, electroencephalograms were made weekly before and at appropriate intervals after the 9 a.m. dose. During the first three to seven days of withdrawal, electroencephalograms were made twice daily, and sometimes oftener. Thereafter encephalograms were obtained as indicated.

Electrocardiograms (three standard leads and chest lead CV 4) were obtained once during the preliminary period, once a month during the period of chronic administration and once during the period of withdrawal.

The 1937 revision of the Stanford-Binet test of intelligence[15] was given once during the preliminary period (form L) and once during the period of withdrawal (form M). The digit-symbol portion of the Wechsler-Bellevue[16] test of adult intelligence was modified by making six sets of alterations in the order of the symbols. Each time the digit-symbol test was administered, the subject received a different key until all six keys had been given, after which the rotation of keys was begun again. The modification was designed to lessen effects of practice. The digit-symbol test, the Bender-Gestalt test[17] and the "Draw a Man" test[18] were given before and approximately one hour after administration of various doses of the different barbiturates during the preliminary period. These three tests were given before and thirty to sixty minutes after the 9 a.m. dose at intervals of three to seven days during the period of chronic intoxication.

During the withdrawal period, the digit-symbol, the Bender-Gestalt and the "Draw a Man" tests were administered every two or three days until the patients reached levels equal to those obtained during the preliminary period. This battery of tests was given once during the period of recovery (at least thirty days after withdrawal began) and was also administered before and thirty minutes after the

12. Ammon, R.: Die fermentative Spaltung des Acetylcholins, Arch. f. ges. Physiol. **233**:486, 1933.

13. Mendel, B.; Hawkins, R. D., and Nishikawara, M.: Cholinesterase Levels in Plasma and Tissues, Am. J. Physiol. **154**:495, 1948.

14. Isbell, H.; Wikler, A.; Eisenman, A. J.; Daingerfield, M., and Frank, K.: Liability of Addiction to 6-Dimethylamino-4-4-Diphenyl-3-Heptanone (Methadon, "Amidone" or "10820") in Man, Arch. Int. Med. **82**:362 (Oct.) 1948.

15. Terman, L. M., and Merrill, M. A.: Measuring Intelligence, Boston, Houghton Mifflin Company, 1937.

16. Wechsler, D.: The Measurement of Adult Intelligence, ed. 3, Baltimore, Williams & Wilkins Company, 1944.

17. Bender, L.: A Visual Motor Gestalt Test and Its Clinical Use, Research Monographs, no. 3, New York, American Orthopsychiatric Association, 1938.

18. Machover, K.: Personality Projection in the Drawing of the Human Figure, Springfield, Ill., Charles C Thomas, Publisher, 1949.

9 a.m. dose during the period of reintoxication. The Kohs block [19] and Rorschach tests [20] were administered once during the preliminary period, once before the 9 a.m. dose on the eighteenth day of chronic intoxication and once during the period of recovery—about thirty days after withdrawal began. In addition, the Rorschach test was administered once or twice during withdrawal, either on the day following a convulsion or during a psychotic episode.

During the recovery period, all the clinical, psychologic and laboratory tests were repeated once or more, as indicated.

PRELIMINARY PERIOD

The behavior of the subjects was typical of that of any group of former morphine addicts who are living together in an experimental situation. They cooperated fully in all observations, were neat and clean, helped with the housekeeping duties around the ward, played cards and dominoes and got along well together.

During the latter half of the preliminary period the patients became bored and were anxious to begin the experiment. They tried in various ways to persuade the personnel conducting the study to begin the period of chronic administration of the drugs sooner than had been planned and frequently attempted to obtain morphine as a reward for good behavior.

Two patients, S 1 and P 3, were usually gregarious, talkative and subject to frequent shifts in mood. A 5 was withdrawn, quiet and participated little in games and other social activities. P 4 and S 2, though not withdrawn, talked less and had less pronounced changes in mood than did S 1 and P 3.

Effects of Large Single Doses of Barbiturates.—Twice weekly during the preliminary period, the patients were given single doses of the particular barbiturate they were to receive during chronic administration. Doses of 0.2 to 0.3 Gm. of any of the drugs caused such slight effects that they will be omitted from the discussion. Doses of 0.4 to 0.7 Gm. of either pentobarbital or secobarbital sodium, or 0.9 to 1.2 Gm. of amobarbital sodium, produced a marked degree of intoxication. The peak effects were reached approximately thirty, forty-five and ninety minutes after the ingestion of secobarbital, pentobarbital and amobarbital, respectively. Three patients (S 2, P 3 and P 4) became lightly comatose after doses of 0.4 to 0.6 Gm. of secobarbital or pentobarbital sodium. S 1 and A 5 did not lose consciousness, even though

19. Kohs, S. C.: Intelligence Measurement: A Psychological and Statistical Study Based upon the Block-Design Test, New York, The Macmillan Company, 1923.

20. Klopfer, B., and Kelley, D. M.: The Rorschach Technique: A Manual for a Projective Method of Personality Diagnosis, Yonkers-on-Hudson, N. Y., World Book Company, 1942. Beck, S. J.: Rorschach's Test: I. Basic Processes, New York, Grune & Stratton, Inc., 1944; Rorschach's Test: II. A Variety of Personality Pictures, New York, Grune & Stratton, Inc., 1947.

they received 0.7 and 1.2 Gm. of secobarbital and amobarbital sodium, respectively. All patients had difficulty in thinking and deterioration in their ability in performing the psychologic tests. Nystagmus, incoordination, ataxia in gait and station, dysarthria and coarse tremor of the hands were constantly observed. The pupillary and deep reflexes were little affected. The abdominal and cremasteric reflexes were consistently depressed, and sometimes absent. A transient Babinski sign and ankle clonus were occasionally detected. P 3 and S 2 became garrulous, boisterous and silly; S 1 and A 5 became quiet, seemed depressed and made desperate efforts to suppress signs of intoxication. The behavior of P 4 was not greatly altered. Regardless of the drug used, signs of intoxication began to diminish within two hours after the drug was administered, and after four to five hours all clinical evidence of intoxication had disappeared. The patients slept poorly on the nights following these large doses, and on the subsequent day they were nervous and tremulous and complained of anorexia and headache. They compared these symptoms to a "hang-over" after an alcoholic debauch.

These large doses of barbiturates had very little effect on pulse and respiration rates, respiratory minute volume, blood pressure and rectal temperature. Such changes as did occur were probably attributable to sedation. Two patients had a periodic type of respiration but continued to maintain their respiratory minute volume at the control level. It was hoped that the data collected on the effects of single doses would be useful in determining whether tolerance developed to any of the effects of the barbiturates during the period of chronic administration. Owing to the marked cumulation and variation of the effects of the drugs during chronic administration, the data were of little use for this purpose.

CHRONIC ADMINISTRATION OF BARBITURATES

Dosage.—After the preliminary observations had been completed, the patients began to receive barbiturates daily. Initially, 0.2 Gm. was administered every twelve hours, and the number of doses and the amount given per day were cautiously increased until, after fourteen to twenty-one days, the patients were continuously exhibiting signs of mild to severe intoxication. The dose was maintained at the level reached on the fourteenth to the twenty-first day for thirty to fifty-three days, after which the dose of 4 of the subjects were again increased. Patient P 4 was so intoxicated on a total dose of 1.3 Gm. of pentobarbital sodium daily that this level was maintained throughout the experiment. Patient S 1 was unable to tolerate an increase in the dose of secobarbital sodium of from 1.3 to 1.6 Gm. daily; so his dose was

reduced to 1.3 Gm. daily for the remainder of the experiment. The dosage schedule during the period of chronic administration is summarized in table 1.

Behavior.—In the early part of the period of chronic administration, when the patients were receiving less than 0.8 Gm. of pentobarbital sodium or secobarbital sodium or less than 2.0 Gm. of amobarbital sodium daily, little evidence of intoxication was observed, and the behavior of the patients differed little from that seen during the preliminary period. At first they were elated over starting the experiment, but after a few days they were disgruntled because of the low degree of intoxication. They repeatedly requested a more rapid increase in the dose and tried various schemes designed to achieve this end. After the dose had been raised to more than 0.8 Gm. of secobarbital or pentobarbital sodium, or to more than 2.0 Gm. of amobarbital sodium, signs

TABLE 1.—*Summary of Dosage During Chronic Barbiturate Intoxication*

Patient	Drug	Period of Drug Administration, Days	Dose: Grams per Day During Chronic Administration *		Total Amount of Drug Taken, Gm.
			1st to 21st Day	22d Day to End of Period	
S 1	Secobarbital (seconal®) sodium.....	92	0.4-1.3	1.3-1.6	110.1
S 2	Secobarbital sodium	132	0.4-1.6	1.6-1.8	214.3
P 3	Pentobarbital sodium	119	0.4-1.3	1.3-1.8	175.3
P 4	Pentobarbital sodium	144	0.4-1.3	1.3	177.7
A 5	Amobarbital (amytal®) sodium.....	104	0.4-3.0	3.0-3.8	310.2

* The total daily dose was divided into five doses. At 5 a. m. a small "eye opener" dose of 0.1 to 0.2 Gm. was given, and larger doses were administered at 9 a. m., 2 p. m., 7 p. m. and 11 p. m.

of intoxication appeared. As the daily dose approached 1.3 to 1.6 Gm. of pentobarbital or secobarbital sodium, or 3.0 Gm. of amobarbital sodium, intoxication became severe. Generally, the signs of intoxication were minimal early in the morning and increased throughout the day, reaching maximum intensity after the 11 p. m. dose.

The behavior of the patients was very similar to the behavior of persons intoxicated with alcohol. They neglected their appearance, became unkempt and dirty, did not shave, bathed infrequently and allowed their living quarters to become filthy. They were content to wear clothes soiled with food which they had spilled. All patients were confused and had difficulty in performing simple tasks or in playing cards or dominoes. They became more irritable and quarrelsome. They cursed one another and at times even fought.

The effects on mood varied from day to day and from patient to patient. S 1, though occasionally euphoric, garrulous and pleasant, was usually depressed, complained of various aches and pains and con-

tinually sought increases in medication, although he was so intoxicated that he frequently could not walk. He would weep over his wasted life and the state of his family but never hinted at suicide. He became infantile and persuaded his friend, S 2, to carry him to bed, button his clothes and feed him. S 1 frequently asked to be released from the experiment but would always change his mind within thirty minutes after missing a dose.

P 3 was frequently elated, hyperactive and garrulous. At other times he was depressed, quiet and withdrawn and talked of the joys of death, but when pressed denied suicidal intentions. He continually attempted to obtain increases in medication. Although he always got along well with other patients when not intoxicated, he became involved in three fights and in a considerable number of cursing matches while taking pentobarbital.

A 5 became even quieter and more withdrawn than he was before receiving amobarbital. He sometimes spent days alone in his room and came out only for meals. He had vague paranoid ideas and stated the belief that the other patients did not like him and that the attendants were showing favor to them. He could not play dominoes without becoming involved in altercations. Some evidence suggestive of homosexual trends appeared. He spoke of giving jewelry to a male patient in one of the dormitories and requested permission to visit this person. He wished to have the jewelry back because the patient had "done him wrong." He obtained embroidered doilies, which he stated were given him by other male patients, who had made them. Although he was the neatest and cleanest of the patients prior to receiving medication, A 5 became the most disheveled during chronic intoxication. He frequently made confused attempts to obtain increases in medication and seemed, as did S 1 and P 3, to be motivated by a desire to become completely unconscious.

S 2 and P 4 showed less pronounced changes in behavior. They continued to maintain good relationships with the other patients and with the attendants, and their personal appearance deteriorated less than did that of S 1, P 3 and A 5. At times S 2 became angry with the other subjects because they teased his friend S 1 over his aches and pains and his infantile behavior. Neither S 2 nor P 4 requested increases in medication. The general picture in both these men was that of a person who was drunk and enjoyed it.

When the dose was increased on the seventy-third day of addiction, the changes already described became severer in P 3. A 5 improved, stayed in his room less, cleaned himself up and expressed fewer paranoid ideas. S 1 became so intoxicated when his dose of secobarbital sodium was increased from 1.3 to 1.6 Gm. daily that he was completely

helpless and had to be carried to bed, dressed, fed and nursed continually. When S 1's dose was reduced to the original level of 1.3 Gm. per day, he became hostile and paranoid and cursed the attendants and other patients. S 2 was more intoxicated but showed little change in behavior after his dose was raised from 1.6 to 1.8 Gm. per day. P 4's dosage was continued at the same level throughout the period of chronic administration.

Changes in Psychologic Tests.—Digit-symbol Test: Four of the subjects (S 1, P 3, P 4, and A 5) showed a rapid decline in ability to perform the digit-symbol test as the dose was increased during the first part of the experiment. The low point in efficiency was reached within thirty days after the onset of chronic intoxication. Thereafter, efficiency in performing the test increased. When the doses were increased later in the experiment, efficiency declined. S 1, who had

TABLE 2.—*Results Obtained with Stanford-Binet Intelligence Test in Preliminary and in the Recovery Period*

Subject	Intelligence Quotient	
	Preliminary Period	Recovery Period
S 1	87	86
S 2	93	111
P 3	90	106
P 4	81	82
A 5	114	119

compulsive personality traits, showed a continual increase in ability to perform the digit-symbol test throughout the experiment. Scores after the drug was administered were usually, but not always, lower than the premedication scores. The results, especially the postmedication scores, fluctuated greatly from one administration to the next. These fluctuations were partially correlated with variations in food intake, as will be explained later. The results showed that the speed of eye-hand coordination is greatly impaired by barbiturate intoxication. Since the digit-symbol test correlates well with the Wechsler-Bellevue intelligence test, the results also suggested impairment of over-all intellectual functioning during chronic intoxication. This interpretation is reenforced by the clinical findings and the results of other tests.

Kohs Block Test: Results obtained with the Kohs blocks are shown in table three. Three of the 5 subjects (S 1, A 5 and P 4) showed a decrease in performance, whereas S 2 and P 3 showed no change or improvement. Had the test been given after the drug had been administered, a much greater deterioration in performance would doubtless have been revealed.

Bender-Gestalt Test: Characteristic changes occurred in the results obtained with this test. They consisted in disturbances in the integration of parts of the gestalt forms into the whole form and of disorientation of the forms with the background. The changes were usually more pronounced after medication, and striking fluctuations in results occurred in the same patient. In general, the changes observed indicate impairment of sensory and motor functions and impairment of ability to organize.

"Draw-a-Man" Test: Analysis of the results obtained with this test indicated that chronic barbiturate intoxication did not alter the basic personality of the subject. Changes indicative of loss of conscious control, accentuation of pathologic features already present in the personality and regression to a more primitive level of adaptation were observed. Thus, A 5, prior to beginning chronic intoxication, drew

TABLE 3.—*Results Obtained with Kohs Block Test in Various Periods of the Experiment*

	Preliminary Period		Period of Chronic Intoxication		Period of Recovery	
Subject	Raw Score	Mental Age *	Raw Score	Mental Age *	Raw Score	Mental Age *
S 1	29	10 - 4	20	9 - 3	29	10 - 4
S 2	92	15 - 2	103	16 - 1	110	16 - 9
S 3	60	12 - 11	60	12 - 11	87	14 - 10
P 4	32	10 - 8	25	9 - 11	37	11 - 1
A 5	52	12 - 4	47	11 - 11	75	14 - 0

* The first figure in the "Mental Age" columns refers to years; the second, to months.

the female figure unclothed and with abundant hair. The male was drawn clothed. During chronic intoxication, both figures were drawn unclothed. The male figure was given hips of feminine shape, and the hair of the male was similar to that of the female. These changes suggest uncovering of latent homosexual trends and are in accord with the changes observed in the behavior of the patient. The changes observed became more pronounced as chronic intoxication progressed. Differences in the drawings before and after administration of barbiturates were not significant.

Rorschach Test: The patterns obtained with the Rorschach test varied little from those obtained in the preliminary period except for a decrease in contact with reality (diminution in percentage of F+ responses) in all subjects except A 5.

Neurologic Status.—The neurologic signs observed during chronic administration were similar to those seen after single doses in the preliminary period and included confusion, difficulty in thinking, dysarthria, nystagmus, incoordination, ataxia in gait and station, adiadokokinesis,

depression of the superficial abdominal and cremasteric reflexes and peculiar coarse jumping movements of the hands and fingers on extension. The deep reflexes and the pupillary reactions were not altered significantly. The Babinski sign and ankle clonus were occasionally observed in A 5. The neurologic signs were usually detectable, but minimal in degree, before the 9 a. m. dose. They increased in intensity throughout the day and were maximal after the 11 p. m. dose. At this time all the patients would be staggering and unable to walk except by sliding along the walls. In spite of close supervision, they occasionally fell and were injured. S 1 broke two ribs by falling on a chair and lost a finger nail which was caught in a door. P 4 fell and incurred a laceration over his left eyebrow. The patients also tended to be more boisterous and quarrelsome at night, and most fights occurred at that time. It finally became necessary to require all patients to be in bed before the last dose was given and to remain in bed until morning. Great care had to be exercised to prevent patients from smoking in bed and setting fires.

Throughout the period of chronic administrations none of the patients showed behavior or symptoms which would be classed as psychotic. They were always oriented in time, place and person and had no hallucinations or delusions. Occasionally, patients had weird dreams. Near the end of the period of addiction, P 4 dreamed that animals were in his room and the filth was on the floor but, after he was awakened, realized that he had merely had a dream.

Cumulation and Variation of Effects.—Cumulation of effects became pronounced early in the period of chronic administration. During the preliminary period single doses of 0.3 Gm. of secobarbital or pentobarbital sodium or 0.6 Gm. of amobarbital sodium produced barely discernible effects prior to addiction. During the period of chronic administration these same doses produced severe drunkenness.

The effects of the same dose of any of the barbiturates varied widely from day to day in the same subject. At times 0.3 Gm. of secobarbital given at 9 a. m. caused only mild drunkenness in both S 1 and S 2. On other days it produced severe intoxication, and even slight coma. A similar variation in effect was noted after pentobarbital or amobarbital. Investigation revealed that on the days on which severe intoxication occurred the patient ate little breakfast or deferred eating until after the 9 a. m. dose had been given. In further experiments, with single doses and other subjects, it was found that a dose which produced only mild intoxication when administered ninety minutes after a standard breakfast caused severe intoxication, and even coma, if given while the subject was fasting. The patients who were chronically intoxicated were therefore required to eat a full breakfast on test mornings. This

reduced the fluctuation in the effects of the barbiturates but did not completely prevent them. Further investigation is required to determine what factors, other than food intake, influence the degree of effect of the barbiturates.

The amount of drug required to produce severe intoxication also varied widely from subject to subject. S 2 was never as drunk as S 1, although he received 0.3 to 0.5 Gm. more secobarbital sodium per day than did S 1 throughout most of the period of chronic intoxication.

Other Changes.—The average rectal temperatures were depressed about 0.1 C. (0.18 F.) during the first three weeks of chronic administration of barbiturates; thereafter, the average rectal temperatures were the same as during the preliminary period, although the daily fluctuations were greater. The pulse rates were elevated about 10 beats per minute throughout the period of addiction. The respiratory minute volume was unchanged, even though periodic variations in rate and depth of respiration were observed when patients were severely intoxicated. The blood pressure was unchanged. The caloric intake was reduced about 10 per cent, but the body weight increased about 3 per cent. There was surprisingly little effect on sleep. The patients slept only about two hours more daily than in the preliminary period, and this increase was accounted for by longer afternoon naps.

Laboratory Observations.—No significant changes occurred in the constituents of the urine, the hemoglobin level, the total red, white and differential blood cell counts, the nonprotein nitrogen and glucose contents of whole blood, the serum bilirubin levels or the results of the thymol turbidity and cephalin flocculation tests. There were no consistent changes in the levels of total, true and pseudocholinesterase in the serum during chronic administration (or during withdrawal).

Electroencephalograms.—During the first thirty days of chronic intoxication the amplitudes of all waves in the electroencephalogram increased, and the percentage of waves with frequencies of 1 to 6 cycles per second (delta waves) increased. After the first month the slow, or delta, activity almost disappeared and the percentage of waves with frequencies of 15 to 30 cycles per second (beta waves) was greatly increased and the increase in voltage of all waves was maintained (figure, *1*). These changes persisted without change throughout the remainder of the period of chronic intoxication.

WITHDRAWAL SYMPTOMS

During the first twelve to sixteen hours after the last dose of barbiturates had been given, the condition of all 5 patients appeared to improve, confusion lessened and neurologic manifestations almost dis-

appeared. All the patients except S 1 were somewhat depressed and moody. S 1 was euphoric, excited and garrulous at this stage. After the first twelve to sixteen hours the patients began to complain of vague anxiety and increasing weakness. They slept poorly, ate little and exhibited a coarse tremor of the hands and face. Twenty-four to thirty hours after administration of the last dose anxiety became severe and and weakness was so great that the patients could hardly stand or walk. They felt faint on standing and preferred to remain in bed. Tremor increased, and fasciculation of isolated muscle groups was seen in 4 of the subjects. They complained of vague abdominal distress, ate little, and 4 vomited. Vomiting was especially severe in P 3. Increased deep reflexes, increased startle responses, mydriasis and swaying on walking or standing because of weakness were also observed. The patients were mentally clear and well oriented and showed no evidence of hallucinations or delusions at this time. Disturbances in making cardiovascular

TABLE 4.—*Cardiovascular Responses to Postural Changes in Patient A 5* *

		Lying Down			Standing, Minutes														Lying Down 0-1 Min.		
					0-1			1-3			3-5			5-7.5			7-5.11				
Period	Day	S	D	P	S	D	P	S	D	P	S	D	P	S	D	P	S	D	P	S	D	P
Withdrawal	4th	112	78	82	X	X	160	X	X	160	Y	Y	Y	Y	Y	Y	Y	Y	Y	Z	Z	Z
Withdrawal	5th	146	92	100	Z	Z	Z	110	80	156	118	100	108	107	90	154	108	90	156	138	92	80
Withdrawal	11th	134	82	80	113	83	114	138	100	106	138	98	102	Z	Z	Z	136	100	100	134	90	108
Recovery	90th	128	82	80	128	84	120	124	92	112	134	95	108	126	96	Z	125	98	120	148	82	72

* S indicates systolic pressure; D, diastolic pressure; P, pulse rate; X, that the blood pressure could not be determined by the auscultatory method; Y, that the patient could not continue standing because of faintness; Z, that no observation was obtained.

adjustments on standing were noted in S 2, P 3, P 4 and A 5. No observations were made on S 1, and no control readings were obtained prior to chronic intoxication. The changes observed were similar to those seen during and after severe febrile illnesses and consisted in a considerable elevation of the pulse rate, a decrease in systolic blood pressure and either a decrease or an increase in diastolic pressure whenever the patient stood, or even sat up. Some of the observations recorded on A 5 are shown in table 4.

Four of the patients had convulsions after the following periods of abstinence: S 1, thirty-nine and one hundred and fifteen hours; P 3, thirty-seven hours; P 4, sixty hours, and A 5, thirty, thirty-three and thirty-nine hours. S 2 did not have a convulsion. Seizures occurred not only when patients were standing but also when they were sitting or lying. They did not recall that convulsions were preceded by an aura. Seizures were typical tonic-clonic type and were clinically indistinguishable from grand mal fits due to idiopathic epilepsy. The convulsions were usually over within three minutes. A transient Babinski sign and

ankle clonus were detected immediately after the convulsions in S 1 and A 5. The patients were usually conscious within five minutes after the onset of the convulsion. They were confused and disoriented for an hour or so, but prolonged stupor did not occur. The patients did not remember the convulsions and termed the episodes "black-outs."

Sixteen hours after he had received his last dose of amobarbital, A 5 experienced numerous episodes of clonic twitching of the extremities, which could be precipitated by external stimulation, such as loud noises, turning on of lights or a light touch. These were not associated with loss of consciousness. A 5 continued to have these symptoms at frequent intervals until the first grand mal convulsion occurred, after which they disappeared. Between the first and the second grand mal convulsion, S 1 frequently had attacks of athetoid writhing movements of the arms and hands. After the movements started, S 1 would hyperventilate and complain of numbness and tingling of the fingers and toes and of cramps in the muscles. The latter symptoms were probably due to alkalosis, resulting from the hyperventilation. It was difficult to determine whether the episodes in this case represented incomplete seizures or hysterical reactions.

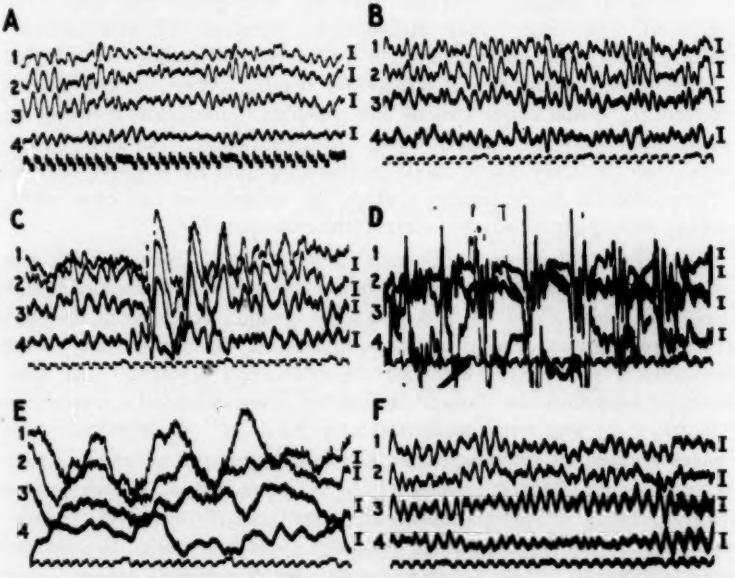
Electroencephalograms During Withdrawal.—During the first twelve to forty-eight hours of withdrawal, paroxysmal bursts of high amplitude, slow waves (4 to 6 cycles per second) appeared in the electroencephalograms of all 5 patients (figure, *1*). The appearance of the paroxysmal slow waves preceded the grand mal seizures. One electroencephalogram was obtained during the clonic phase of a convulsion (figure, *1 D*) and was characterized by bursts of high amplitude, fast waves (spikes of frequencies of 30 to 50 cycles per second). After seizures, slow, "stupor" waves (1 to 6 cycles per second) appeared (figure, *1 E*). Although increased percentages of waves of frequencies of 6 to 7 cycles per second persisted about two weeks, the electroencephalograms rapidly became normal after convulsions ceased. One month after the beginning of withdrawal the electroencephalograms were indistinguishable from those obtained in the preliminary period.

Psychologic Effects.—After grand mal seizures, the patients were usually less apprehensive for a short time. Thereafter, anxiety reappeared and increased, tremor became more prominent, weakness continued, disturbed cardiovascular responses on standing persisted and the patients slept and ate poorly. In A 5 a psychosis did not develop, and his symptoms gradually disappeared over the course of about ten days.

In S 1, S 2, P 3 and P 4 psychoses developed. All these patients experienced insomnia during the twenty-four to forty-eight hours which preceded delirium. After definite signs of the psychoses appeared, the rectal temperature rose 0.5 to 1.0 C. (0.9 to 1.8 F.), respiration and

pulse rates were increased and the blood pressure rose. These changes were most pronounced at the height of delirium, decreased as the psychosis abated and may have been caused by anxiety and restlessness during the psychotic episodes.

During the fourth night of withdrawal, S 1 lay awake giggling in a silly fashion, staring at the walls and talking with nonexistent persons. At this time he was oriented for time, place and person and, despite the unmistakable evidence, denied that he was experiencing hallucinations. During the following day he was very apprehensive and occa-



Effects of chronic pentobarbital intoxication on the electroencephalogram. Monopolar and bipolar recording. All monopolar tracings are from the left side. *1*, frontal to ear lead; *2*, parietal to ear lead; *3*, occipital to ear lead; *4*, occipital to occipital lead.

A, a normal (control) electroencephalogram; *B*, tracing on one hundred and seventh day of intoxication, showing increase in amplitude and beta activity; *C*, tracing thirty-five and one-half hours after withdrawal, showing spikes and paroxysmal slow waves; *D*, tracing thirty-seven hours after withdrawal, showing seizure discharge; *E*, record thirty-seven hours after withdrawal, showing post-seizure stupor waves; *F*, record one month after beginning of withdrawal, showing return to the control record.

Calibrations: 23.8 microvolts, except in *D*, in which it is 126.5 microvolts; time is expressed in seconds and tenths of seconds.

sionally shouted, "Who's that out there?" or, "Did you call me?" He attempted to wash the walls of the rooms, through he had no water and no washcloth. He continued to be oriented in all spheres. Dur-

ing the fifth night of withdrawal the psychosis became severer. He thought that a railroad ran through the ward. He conversed with the trainmen about repairs to the locomotive and made trips to South Carolina with a trainload of goats. On the following day he was still oriented in time, place and person but was apprehensive and frightened and begged for morphine and barbiturates. He admitted that he had been experiencing hallucinations but appeared to realize that they were imaginary, and not real. During the sixth night of withdrawal he became disoriented in time and place but not in person. He thought that he was in various places in South Carolina and that he was riding trains; he became agitated because he imagined that persons were trying to harm him. He was blown up three times, was cut with knives, etc.; several imaginary persons were murdered during the night; he saw tiny men descending in parachutes; an old woman was perched on the ceiling of the room; shimmering rings of light or smoke which floated in the air went in one of his ears, and he pulled them out the other ear. He misidentified persons and objects. During the sixth day he was disoriented in time and place but retained his identity. He had visual and auditory hallucinations constantly, was extremely agitated and constantly tried to escape from his imaginary persecutors. He stated the belief that one of the physicians and two of the attendants had done various evil things to him, and he threatened them with bodily harm and prosecution for their crimes. All these symptoms persisted unabated until the ninth night. At that time the patient was very excited; he had a temperature of 38.3 C. (100.9 F.) and a pulse rate of 140. It appeared that he was becoming dangerously exhausted; so withdrawal was terminated. A total of 1.1 Gm. of secobarbital sodium was administered in divided doses before the patient slept. On the following day he was returned to his usual dose of 1.3 Gm. daily. Hallucinations occurred at infrequent intervals during the first day after restoration of barbiturate administration. On the second day hallucinations were no longer present, although the patient still believed that the hallucinations he had experienced had been real and asked that the police be called to arrest the persons who had committed the murders. On the third day after being returned to secobarbital medication, S 1 realized that all his experiences were imaginary and was greatly relieved. Secobarbital was very slowly withdrawn during the succeeding thirty-day days, and convulsions and the psychosis did not recur.

The results of a Rorschach test, administered on the third day of withdrawal, showed few quantitative differences from those of the control test except for a decrease in the percentage of F+ responses. Another Rorschach test, administered while the patient was having hallucinations, showed a great increase in the total number of responses.

This was due to increases in the number of responses in the large (D) and small (Dd) detail areas. The number of responses scored as human fantasy (M) and animal fantasy (FM) also increased. These changes reflected the psychotic behavior of the patient.

S 2 had no convulsions but slept very little during the third and fourth nights of withdrawal. At 3 a. m. of the fifth day, he awoke and demanded examination by a physician. He said he had "knots" in his head and in his muscles. He expressed the belief that his brain had been jarred loose and dropped down into his body. He wanted an electroencephalogram taken to determine what was wrong. While the electrodes were being attached, he began to laugh, giggle and speak to nonexistent people. Later, he said that the "brain wave" machine had been reversed and had put brain waves into his head, instead of taking them out. This situation was remedied by taking another electroencephalogram. Throughout the day the patient had varied auditory and visual hallucinations. He lay quietly grinning and smiling, staring at the wall and talking to nonexistent persons. When questioned sharply, he appeared startled, stopped watching the wall, answered questions and, superficially, appeared to be well oriented. As he answered questions, his attention would wander, he would stare at the wall and stop talking in the middle of a sentence. He imagined seeing women, men, giants, animals and airplanes. He saw himself, or part of himself, on the wall. When asked how he could be in two places at once, he said, "It is funny; I don't see how it is possible, but it is done by a system. They use pictures." Some of the hallucinations appeared to be sexual. The patient said, "Now he's putting it in her. They're all doing it to her." At times he hyperventilated spontaneously but would stop on command. The hallucinations appeared to become more vivid as the day progressed. When night came, the patient became unresponsive, would not answer questions and appeared to be completely out of contact with reality. He lay on the bed posturing and grimacing and watching the wall. He appeared to be leading a band, using a pocket comb for a baton, and said, "Isn't that beautiful music?" He became wildly excited and beat the bed with his hands and fists. As the night wore on, he began to rave wildly and incoherently. He seemed to be accusing his wife of sexual irregularities and threatening her. He attempted to masturbate but could not obtain an erection or an orgasm, but would urinate and soil himself. The following day he improved somewhat and seemed to be superficially oriented. He spent most of the sixth day of withdrawal watching the walls, laughing, talking to imaginary persons and listening to imaginary music. This behavior continued through the sixth night and through the morning of the seventh day. At noon on the seventh day the

patient fell asleep. On awakening, five hours later, he jumped from his bed, eluded the attendants and ran out of the room. He went to the bathroom, washed his face, combed his hair and changed pajamas. He was hostile and belligerent. He seemed to feel that his hallucinations were associated with the room where he had been kept during withdrawal. He bathed several times, changed pajamas repeatedly and swept the floor. He was allowed to remain in the open ward and after three hours became calm and again slept. On awakening the next morning, he was not experiencing hallucinations, was quiet, oriented in all spheres, but somewhat hostile and withdrawn. He said he had "blown his stack" but that he was better. He described some of the hallucinations he had experienced but did not remember those involving sex. He stated that his hallucinations were caused by control of his thoughts by the attending physicians, who used a movie projector or the "power of suggestion" to accomplish this purpose. The patient slept well on the seventh night, and on the eighth day no evidence of a psychosis was present. He realized that his hallucinations were imaginary and that they were due to a physiologic disturbance precipitated by withdrawal of barbiturates, and not by control of his thoughts by any person.

A Rorschach test administered during the fifth day, while S 2 was experiencing hallucinations, showed a decrease in the total number of responses, failure to make use of small detail areas and very little change in fantasy percepts, despite the fact that he was hallucinating. The results suggest a breaking down of his compulsive, constrictive mechanisms.

The manifestations of the psychosis were much less dramatic in the case of P 3. He slept very little during the fourth and fifth nights of withdrawal and appeared to talk to nonexistent persons. However, he was never disoriented in any sphere and stoutly maintained that he was not experiencing hallucinations. Between the seventh and the twelfth day of withdrawal he slept well and no overt evidence of hallucinations was detected. On the thirteenth and fourteenth days he was very restless and agitated, did not sleep, was confused at times and talked to nonexistent persons. He remained oriented in all spheres and continued to deny the presence of hallucinations. On the fifteenth day, agitation disappeared. He slept through most of the fifteenth, sixteenth and seventeenth days, and no further evidence of a psychosis was observed. About a month later, P 3 admitted having both auditory and visual hallucinations during withdrawal.

A Rorschach test obtained on the third day of withdrawal showed perseveration with an increase in the percentage of animal percepts.

An increase in responsiveness to color indicated heightened emotionality. No Rorschach test was obtained during the time when hallucinations were probably present.

Immediately after the convulsion, which occurred at the sixtieth hour of withdrawal, P 4 was confused and disoriented in time and place but not in person. He thought that he was in various towns in Oklahoma, Texas and New Jersey and that it was July instead of June. He was able to identify persons and objects correctly. He stated that someone was poisoning him with atropine. During the third night of withdrawal he was completely disoriented and would not answer questions. He lay quietly, stared at the wall and held unintelligible conversations with imaginary persons. He masturbated twice during the night. During the fourth day, he was very quiet, regained his orientation, was somewhat confused and was reluctant to talk about his hallucinations. Thereafter, P 4, though weak and tremulous, did not appear to be psychotic and improved rapidly. By the tenth day of withdrawal, he was willing to describe some of his hallucinations, which included small persons, animals, snakes and absent persons.

A Rorschach examination, obtained on the third day of withdrawal of the drug, when the patient was overtly psychotic, showed a decrease in form control responses (F+), an increase in the number of animal responses (A), no increase in human (M) or animal fantasy (FM) responses and a decrease in ability to organize.

Although A 5 had three grand mal seizures, no evidence of a psychosis was detected. He was confused and disoriented for an hour or so after the convulsions occurred but did not show any evidence of hallucinations or delusions. He improved rapidly, and ten days after the beginning of withdrawal he seemed completely well.

The results obtained with the Bender-Gestalt, "draw-a-man" and digit-symbol tests all returned to the levels seen during the preliminary period within sixteen days after withdrawal began, except in the case of S 1, who had to be returned to administration of barbiturates on the ninth day of withdrawal.

Laboratory Observations During Withdrawal.—No significant changes occurred in the red blood cell count, hemoglobin level or results of the hepatic function tests during withdrawal. All patients had a mild hyperglycemia, which was most pronounced during the psychotic phase. The nonprotein nitrogen content of the blood of S 1 and P 3 was 54 and 53 mg., per hundred cubic centimeters, respectively, on the third day of withdrawal. The highest values observed for S 2 and P 4 were 42 and 43 mg., respectively, per hundred cubic centimeters. Albumin and hyaline casts were present in the urine of P 3 on the third and fourth days of withdrawal. No other significant changes were observed

in the urine of any of the other patients. There was a tendency for the total white blood cell count to increase during the first seven days of withdrawal. The highest count (S 2), of 14,600 cells per cubic millimeter, was obtained during the seventh day of abstinence.

RECOVERY

All the patients recovered completely. From sixty to ninety days after withdrawal was begun, no evidence of residual damage could be detected by physical, psychiatric, laboratory or psychologic examinations (tables 2 and 3). Weakness, which was the chief symptom at the end of the period of withdrawal, gradually disappeared, and six to twelve weeks after withdrawal began all patients felt as well as they did before beginning the experiment.

REINTOXICATION

Sixty to ninety days after withdrawal began, 4 patients (S 2, P 3, P 4 and A 5) were abruptly placed on the same dosage of barbiturates they were receiving when withdrawal began. S 1 had insufficient time remaining prior to his discharge from the institution to permit his use as a subject in this phase of the experiment. Reintoxication was carried out to determine whether the patients could tolerate the maximum dose of barbiturates they had received during chronic administration without approaching that dose gradually. All 4 patients became so intoxicated during the first twenty-four hours that the experiment had to be terminated. The degree of intoxication, as judged by observations on behavior, changes in neurologic status and psychologic tests, was far greater than at any time during chronic administration. In fact, it would have been dangerous to the lives of these subjects to continue administration of barbiturates at the same dosage they had attained during chronic intoxication.

COMMENT

It is obvious that chronic barbiturate intoxication is a dangerous and undesirable condition, which is very similar to chronic alcoholism. Persons who take large amounts of barbiturates are confused, are unable to think clearly and have poor judgment. Their emotional control is impaired, and pathologic features in their personalities are accentuated; they become hostile, and even assaultive, over fancied insults or minor incidents, and they regress and behave like small children. At times they are so depressed that suicide becomes a distinct possibility. Because of the motor incoordination produced by the barbiturates, patients frequently fall and may be seriously injured. They also are likely to fall asleep while smoking and set serious fires. They are

unable to work and would be a serious menace if they attempted to drive automobiles. The judgment of persons taking large amounts of barbiturates is so impaired that they are likely to take additional doses of the drugs, even though they are already dangerously intoxicated. This could easily lead to an overdose and to death. It is possible that many deaths from barbiturate intoxication which are recorded as suicides are involitional and may represent superimposition of acute barbiturate poisoning on a preexisting chronic intoxication.

Owing to the wide fluctuation of effects from day to day during chronic administration of barbiturates, it was difficult to determine whether any significant degree of tolerance had developed. When the men were abruptly placed on the same dosage of barbiturates they had been receiving prior to withdrawal, they became much more intoxicated than at any time during chronic administration. It seems clear, therefore, that some tolerance was acquired. The degree of tolerance to the barbiturates is, however, not nearly so great as is tolerance to morphine.

The results confirm the literature respecting the occurrence of convulsions and psychoses following abrupt withdrawal of barbiturates from persons chronically intoxicated with these drugs. In the light of the present experiment, these symptoms cannot be attributed to a combination of intoxications, to malnutrition or to a combination of intoxications and malnutrition. Furthermore, the occurrence of convulsions following withdrawal of barbiturates is not dependent on the existence of an epileptic diathesis. None of these subjects had any personal or family history of epilepsy, and all had normal electroencephalograms. The results of my associates and myself with respect to the serum cholinesterase content are at variance with those of Schütz,[21] who reported depression of the serum cholinesterase level during chronic administration of barbiturates and attributed the occurrence of convulsions to a resultant accumulation of acetylcholine. Schütz used a titrimetric method for determination of the total serum cholinesterase content, whereas we employed a manometric method. Whether the difference in results is due to a difference in methods used is unknown. The results also show that during abstinence delirium develops in persons who had never been psychotic prior to chronic intoxication with barbiturates. Although the number of cases is too small to permit one to draw conclusions, it is interesting that the psychoses were severer in the 3 subjects (S 2, S 1 and P 4) who, according to their Rorschach examinations, had a great deal of constricted, nonemotional type of responsiveness; and, on the other hand, psychoses did not occur or

21. Schütz, F.: Mechanism of Drug Addiction and Drug Tolerance, Nature, London **148**:725 (Dec. 13) 1941.

were mild in the 2 subjects (A 5 and P 3) who were much less constricted and responded affectively or with fantasy. The experiment suggests that if a psychosis develops during withdrawal of barbiturates, the manner in which the patient reacts to his psychosis may be related to his basic personality structure. Thus, S 1, who was an anxious, hysterical person, was greatly agitated and apprehensive while he was hallucinating, whereas P 4, who had very little anxiety, was not agitated during the delirium.

The opinion, which has been widely held, that abrupt withdrawal of barbiturates is not followed by untoward symptoms [22] is not tenable. Convulsions and psychoses did not occur in any of our patients until the drug was withdrawn. This result is in accord with our clinical experience. We have never seen convulsions and/or psychoses develop in persons addicted to barbiturates unless the drug was abruptly withdrawn or suddenly reduced to 50 per cent or less of the dose the patient was accustomed to take. Like the state following withdrawal of morphine, the withdrawal of barbiturates produces a clearcut clinical entity, which follows a definite pattern and runs a definite course. The barbiturate withdrawal syndrome might be defined as a disorder due to sudden reduction in the dose of barbiturates which a person chronically intoxicated with those drugs is accustomed to take, and which is characterized by weakness, anxiety, anorexia, insomnia, tremor, disturbances in cardiovascular adjustments on standing, convulsions, slight fever and a psychosis. One can surmise, since patients recover completely, that the barbiturate withdrawal syndrome is due to a reversible disturbance in the central nervous system, and not to permanent anatomic changes.

The development of signs of abstinence on withdrawal of the drug is not a characteristic which is specific for any particular barbiturate. In our experiment, convulsions occurred in patients who had received amobarbital, pentobarbital or secobarbital, and psychoses were observed after the withdrawal of pentobarbital and secobarbital. Reports in the literature show that convulsions or a psychosis or both have occurred after withdrawal of barbital, phenobarbital, pentobarbital, amobarbital and cyclobarbital (phanodorn). Whether the syndrome is more easily produced and is severer after intoxication with any particular barbiturate

22. Tatum, A. L.: The Present Status of the Barbiturate Problem, Physiol. Rev. **19**:472 (Oct.) 1939. Lowry, O.: A Comparative Study of the Habitual Use of Barbiturates and Coal-Tar Derivatives as Furnished by Reports from Various Hospitals Throughout the United States, Canad. M. A. J. **31**:638 (Dec.) 1934. Goldstein, S. W.: Barbiturates—Are They Narcotics? J. Am. Pharm. A. (Scient. Ed.) **36**:97 (April) 1947. Gillespie, R. D.: On the Alleged Dangers of the Barbiturates, Lancet **1**:337 (Feb. 17) 1934. Weiss, S.: The Clinical Uses and Dangers of Hypnotics, J. A. M. A. **107**:2104 (Dec. 26) 1936.

is unknown, although Pohlisch and Panse [9] found that psychoses occurred more frequently after withdrawal of cyclobarbital than after withdrawal of barbital or phenobarbital.

The similarity of the barbiturate withdrawal syndrome to alcoholic delirium tremens is striking and has been commented on by various observers, notably Kalinowsky,[10b] Pohlisch and Panse [9] and Meyer.[8j] In both conditions, weakness, tremors, anxiety, insomnia, convulsions and a psychosis are prominent features. In both, the psychosis is preceded by insomnia and is characterized by disorientation in time and place but not in person, by hallucinations which are predominantly visual, by a tendency for the psychosis to begin and to become worse at night and by rapid improvement, which occurs after return of the ability to sleep. Similar clinical pictures have been described after withdrawal of chloral or paraldehyde from patients chronically intoxicated with these drugs.[23] It is likely that delirium tremens is not a syndrome which is caused by chronic alcoholic intoxication only, but represents a physiologic derangement which may follow chronic intoxication with a variety of hypnotic drugs. If this is true, it should be possible to substitute one hypnotic drug for another without signs of withdrawal appearing, just as methadone, a drug which has pharmacologic actions similar to those of morphine, can be substituted for morphine without signs of withdrawal appearing. The possibility of substitution of one drug for another, as Kalinowsky [10b] pointed out, may explain why delirium tremens rarely occurs after abrupt withdrawal of alcohol from patients with chronic alcoholism in hospitals, since such patients are almost universally given some hypnotic medicament, most frequently paraldehyde, which is then usually slowly withdrawn.

The barbiturates are addiction forming in every sense of the word. Prolonged use causes great harm to the user and to society. Although the degree of tolerance is less in barbiturate intoxication and the manifestations of physical dependence on barbiturates are different from those of dependence on morphine, the phenomena characteristic of addiction to the opiates—habituation, or emotional dependence, tolerance and the appearance of signs of abstinence after withdrawal of the drug—are all present with chronic barbiturate intoxication.

The manifestations of chronic barbiturate intoxication are, in most ways, much more serious than those of addiction to morphine. Morphine causes much less impairment of mental ability and emotional control

23. de Clérambault, G.: Délires de cause chloralique, Ann. méd.-psychol. **10**,s.9:33, 1910; Du diagnostic différentiel des délires de cause chloralique, ibid. **11**,s.9:220, 1909. von Krafft-Ebing, R.: Ueber Paraldehyd-Gebrauch und Missbrauch nebst einem Falle von Paraldehyd-Delirium, Ztschr. f. Therap. m. Einbzhng. d. Elect.-u. Hydrotherap. **5**:49-52, 1887; Therap. Monatsh., 1887, p. 244. Nothass: Paraldehydpsychosen, Allg. Ztschr. f. Psychiat. **76**:826, 1920. Pohlisch.[8c]

and produces no motor incoordination. Furthermore, such impairment as does occur becomes less as tolerance to morphine develops, and withdrawal of morphine is much less dangerous than is withdrawal of barbiturates.

SUMMARY AND CONCLUSION

Five men formerly addicted to morphine, who volunteered for the experiment, received doses of secobarbital (seconal®), pentobarbital or amobarbital (amytal®) sufficiently large to induce continuous mild to severe intoxication for periods varying from ninety-two to one hundred and forty-four days.

Symptoms of chronic barbiturate intoxication included impairment of mental ability, confusion, regression, increased emotional instability, nystagmus, dysarthria, ataxia in gait and station and depression of the superficial abdominal reflexes. The clinical manifestations of chronic barbiturism were similar to those of chronic alcoholism.

The effects of the same dose of barbiturates varied greatly in the same person from day to day. This variation was partially correlated with changes in food intake. Pronounced differences in the effects of the same dose of barbiturates on different subjects were also observed.

Although the variation in the effects of the drugs made it difficult to determine whether tolerance developed, 4 of the 5 patients, when abruptly returned to the same dose of barbiturates they were receiving at the end of the experiment, became much more intoxicated than they were at any time after attaining the maximum dosage level gradually. Some tolerance, therefore, developed during chronic intoxication.

After abrupt withdrawal of barbiturates, a definite abstinence syndrome developed. The barbiturate withdrawal syndrome was characterized by disappearance of the signs of intoxication, weakness, tremor, great anxiety, anorexia, nausea and vomiting, rapid loss of weight, increase in pulse and respiration rates, fever, increase in blood pressure, difficulty in making cardiovascular adjustments in standing, convulsions of grand mal type and the development of a psychosis. The barbiturate withdrawal psychosis resembled alcoholic delirium tremens and was characterized by anxiety, agitation, insomnia, confusion, disorientation chiefly in time and place but not in person, delusions and auditory and visual hallucinations.

No changes were observed in the total, true or pseudocholinesterase contents of serum during chronic intoxication with barbiturates or after withdrawal.

Recovery from chronic barbiturate intoxication and from the barbiturate withdrawal syndrome appeared to be complete. No clinical evidence of permanent damage was detected sixty days or more after withdrawal began.

During chronic barbiturate intoxication, the amplitude of all electroencephalographic waves was increased, and the percentage of waves of frequencies of 15 to 30 cycles per second was greater. After withdrawal of barbiturates, paroxysmal bursts of high amplitude waves of frequencies of 4 to 6 cycles per second appeared in the first twelve to forty-eight hours. Records obtained during and after a convulsion were similar to records of grand mal seizures due to idiopathic epilepsy. Within thirty days after the barbiturates were discontinued, the electroencephalographic pattern returned to that seen prior to chronic intoxication.

Barbiturates are addiction-forming drugs, and in some respects addiction to barbiturates is more dangerous and undesirable than is addiction to morphine.

ADAPTIVE BEHAVIOR IN LONG-SURVIVING DOGS WITHOUT NEOCORTEX

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THE TWO chronic decorticated dogs whose behavior is discussed in this paper were the last of a series of such preparations which were used in studies on morphine and methadone addiction. The data acquired in the studies on drug addiction have been summarized elsewhere.[1] In the course of these investigations detailed observations on the behavior of these preparations were made, both in the ordinary laboratory environment and in formal conditioned reflex situations. Anatomic studies of the brains of these animals showed that all traces of neocortex had been removed at operation. The data are presented here as a contribution to the problem of the role of the neocortex in acquired adaptations.

METHODS

Dog 66 was a short-haired black female mongrel about 18 months old, weighing about 9 Kg. Dog 75 was a short-haired white male mongrel of similar age and weight. Both animals had been housed in the animal quarters for several months prior to operation but had not been subjected to any training procedures. The technic of operation was the same for both animals, with minor variations.

Operation was performed, with aseptic technic, in the animal under anesthesia produced by intravenous injection of pentobarbital sodium. After preparation of the scalp in the usual manner, a curved incision was made on the side of the head parallel with and close to the midline, and the scalp and superficial muscles were reflected. An osteoplastic flap was then turned down, the procedure requiring fracture of the temporal bone. The exposure was made as large as possible. A U-shaped incision was then made in the dura with the base medially, and the dura was then reflected back, exposing the parieto-occipital cortex. Ablation of the hemisphere was then carried out by the use of suction and spatula, the glistening white hippocampus serving as a guide. The spatula was first inserted into the lateral ventricle alongside the hippocampus and directed rostrally and medially. An upward incision was then made through the corpus callosum, after which the spatula was reinserted in the same way and a downward incision executed. Remnants of the temporal, occipital and frontal lobes were then removed by suction. Finally, a transverse incision was made in the plane of the junction of the middle and the anterior fossa, and all tissue anterior to this was removed by suction. The hippocampus, thalamus and pyriform lobes were partly removed by this procedure, but

From the Research Division, United States Public Health Service Hospital.

1. Wikler, A.: Recent Progress in Research on the Neurophysiologic Basis of Morphine Addiction, Am. J. Psychiat. **105**:329-338, 1948.

no attempt was made to remove any tissue other than the neocortex. Hemostasis was secured by silver clips, cotton patties soaked in warm isotonic sodium chloride solution and fibrin foam.[2]

After removal of the hemisphere, the dura was resutured with black silk; the bone flap was replaced, and the overlying soft tissues were repaired. The scalp wound was closed with a subcuticular suture of black silk.

After the operation, the animal was given a transfusion of 100 cc. of citrated whole blood. This was obtained by arterial puncture in a donor dog rendered analgesic by subcutaneous injection of morphine sulfate, 25 mg. per kilogram, or methadone, 10 mg. per kilogram.

The dog was kept warm in an incubator until it became restless. It was then removed to a circular pen, the walls of which were made of smooth linoleum and the floors of wire hardware cloth covered with removable linoleum pads and a blanket. The animal was turned frequently until it had fully recovered from the anesthesia. The operation was completed several weeks later by a similar procedure on the other half of the brain.

After recovery from the second (final) operation, each animal was fed solely on slices of fresh hog liver soaked in water,[3] and a supplementary clysis of 200 to 300 cc. of isotonic (0.9 per cent) sodium chloride solution was given daily.

Dog 66 survived nineteen months, and dog 75 twelve months, after completion of decortication. Within an hour after death (which occurred spontaneously in each animal during studies on morphine addiction) the head of each preparation was perfused with dilute solution of formaldehyde U. S. P. (1:4) under a pressure of about 100 cm. of water. The brains were then removed with the dura intact and preserved in dilute solution of formaldehyde U. S. P. of the same strength.[4]

RESULTS

The following protocols summarize the observations on the 2 decorticate preparations. Details of the studies on the effects of drugs are not included.

Dog 66.—June 12, 1946: Left hemidecortication.

June 13: Dog up and walking on all four legs, circling to left along wall of tub; ate from bowl.

September 13: Dog now walked in straight line; no circling.

September 15: Decortication completed by removal of right hemisphere.

September 16: Dog righted head, but attempts to assume upright position not successful. Liver placed in oropharynx was swallowed.

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2. The fibrin foam used in these experiments was supplied by the Harvard Plasma Laboratory, under the auspices of the Office of Scientific Research and Development.

3. Dr. Clinton H. Woolsey, professor of physiology, University of Wisconsin Medical School, gave advice in the feeding and postoperative care of decorticate dogs.

4. The general pathologic examinations (exclusive of the brain) were made by Dr. E. S. Maxwell, Lexington, Ky., consultant in pathology to the United States Public Health Service Hospital. The descriptions of the gross brain specimens were made by Dr. I. Mark Scheinker, assistant professor of neurology, University of Cincinnati College of Medicine. The serial sections of the brains were prepared at the Institute of Neurology, Northwestern University Medical School, and were described by Mr. C. Murphy Combs, fellow, department of anatomy of that institution.

September 19: Dog righted head and body; walked about, circling periodically. Tactile placing and hopping reactions of forelegs absent. Occasionally proprioceptive placing reactions elicited. Furious barking, struggling, pupillary dilatation and lashing of tail when foreleg was pinched or extremities were restrained.

September 24: When removed from tub and placed in corner, dog pushed nose in corner continuously until removed. Walked, crouched and slept alternately during day.

Attempt at Auditory Conditioning: Pure tone of 500 cycles per second (conditioned stimulus) alone evoked only orienting response. Faradic shock to right foreleg (unconditioned stimulus) alone evoked flexion of leg (unconditioned response). No conditioned response observed after 40 trial combinations of conditioned stimulus for five seconds followed by unconditioned stimulus.

September 25: Spontaneous activity observed from 8 p. m. to 4 a. m. Alternate waking and sleeping about every two hours, but intervals rather irregular. Over eight hour period spent about equal time in sleeping and waking.

September 30: Attempt at Auditory-Motor Conditioning, as on September 24: No evidence of conditioning, after 50 combinations of conditioned and unconditioned stimuli.

October 18: Attempt at Tactile Conditioning: Conditioned stimulus, 10 strokes of plastic comb to skin of right hindquarters; unconditioned stimulus, faradic shock to right hindleg, following immediately tenth stroke of comb. No response to conditioned stimulus alone. Unconditioned response consisted of flexion of right hindleg, increased respiratory rate, wagging of head from side to side and, occasionally, barking. No evidence of conditioning during first 200 combinations of conditioned and unconditioned stimuli. Thereafter, irregular head wagging responses (about 1 every 10 trials) during next 100 trials. Interval between trials, one minute.

October 19: Procedure repeated. Twenty-five trials of conditioned stimulus alone; no response. After 70 trials of conditioned stimulus followed by unconditioned stimulus, head wagging responses appeared, as on October 18. No conditioned flexion of leg observed.

October 21: Procedure repeated. No response to conditioned stimulus alone on 6 trials. During next 12 trials of combined conditioned and unconditioned stimuli, head wagging appeared in 10. During next 12 trials, unconditioned stimulus was omitted (extinction). Head wagging response to conditioned stimulus appeared 7 times during this period. During next 21 trials, unconditioned stimulus again followed conditioned stimulus reenforcement). Head wagging in response to conditioned stimulus appeared 15 times. Experiment terminated because of extreme restlessness of preparation.

October 22: Animal placed in light harness in conditioned reflex chamber. Responses to pure tone of 500 cycles per second alone observed. Only orienting responses seen. Toward end of session (one hour) periodic struggling and whining, gradually increasing in intensity and frequency, noted; no relation to exhibition of tone (for five seconds, every minute).

October 24: Attempt at Tactile-Motor Conditioning: Procedure as October 18. No response to conditioned stimulus until trials. Thereafter, incidence of head-wagging responses to conditioned stimulus increased, until it reached 100 per cent at about hundredth trial. Dog progressively more restless.

November 5: Dog very restless and irritable just before defecation; apparently did not avoid obstacles. When allowed to roam about laboratory, collided with pipes, tables and walls. When placed in corner, pushed forward for few minutes,

then circled to left or right a few times and finally extricated self. Did not back up. Seemed to force self into narrow passages when encountering them by chance. Exhibited sham rage when restrained.

November 27: Licked chops when root of tail was scratched lightly.

Jan. 6 to Aug. 9, 1947: Studies on Morphine and Methadone Addiction.

Oct. 20, 1947: Attempt at Auditory-Motor Conditioning: Conditioned stimulus, pure tone of 500 cycles per second, for ten seconds; unconditioned stimulus, faradic shock to left hindleg. Unconditioned response, leg flexion and weak bark; unconditioned stimulus given during last second of conditioned stimulus. Total of 121 trials, at intervals of one minute; no evidence of conditioning. Toward end of test period, animal exhibited periodic excitement, which at times coincided with exhibition of conditioned stimulus.

October 21: Same procedure; 84 trials. Only suggestion of conditioned response occurred toward end of session, when dog was exhibiting periodic bursts of excitement.

October 22: Same procedure, except that duration of conditional signal was reduced to five seconds; 140 trials, in two sessions. Results same as on October 21.

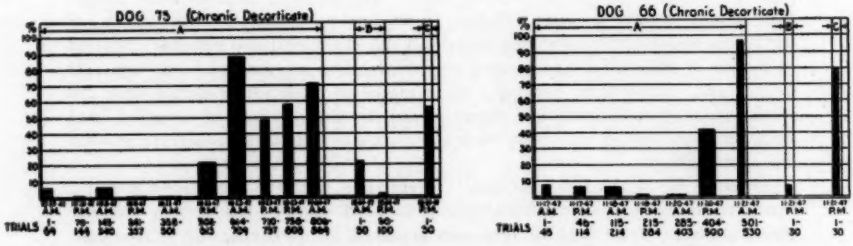

Chart 1.—Percentage of conditioned motor responses to tactile stimuli in dogs without neocortex. For dog 75, *A* indicates conditioning (regular flexion of the hindleg, beginning with trial 604); *B*, extinction (disappearance of flexion of the hindleg, beginning with trial 7); *C*, reenforcement (reappearance of flexion of the hindleg, beginning with trial 5). For dog 66, *A* indicates conditioning (regular flexion of the hindleg, beginning with trial 471); *B*, extinction (disappearance of flexion of the hindleg with trial 3, and *C*, reenforcement of flexion of the hindleg, beginning with trial 2).

October 23: Same procedure; 171 trials. Results as on October 21. Total number of trials 516.

October 27: Same procedure, except that trials were spaced at five minute intervals; 85 trials, in two sessions. Results as October 21. Toward end of session, dog exhibited restlessness every two to three minutes at first, but every one-half minute later. No evidence of time conditioning.

October 28: Same procedure as on October 27; 38 trials. Similar results.

November 3: Attempt to Produce Auditory-Motor Avoidance Conditioning: Pure tone (500 cycles per second) stimuli (23 trials) followed after ten seconds by charging of grid under left hindleg accompanied with buzzing sound from inductorium. No conditioned response to conditioned stimulus, but on 2 occasions left hindleg was held up off grid until buzzing sound ceased.

November 4: Same procedure, continued; 57 trials, no conditioned response.

November 5: Same procedure; 49 trials, no conditioned response.

November 6: Same procedure; 87 trials (total, 216); no evidence of conditioned response. Left leg injured by scratching during excitement at end of period. Experiment terminated.

November 17: Attempt to Produce Tactile-Motor Conditioning (chart 1): Conditioned stimulus, 10 strokes of plastic comb on middle of lower part of back; unconditioned stimulus, faradic shock to left hindleg; unconditioned response, flexion of leg and weak bark. During preliminary trials, head wagging occurred 16 per cent of time in response to conditioned stimulus alone (25 trials). After 114 trials of conditioned stimulus followed by unconditioned stimulus, head wagging appeared 23.2 per cent of time in response to conditioned stimulus. Conditioned leg flexion appeared in only 4.3 per cent of trials.

November 18: Same procedure continued; 169 trials, in two sessions. Head wagging in response to conditioned stimulus noted irregularly in about 10 per cent of trials. Conditioned leg raising (conditioned response) in average of 3.0 per cent of trials.

November 20: First session, 118 trials: Head wagging in response to conditioned stimulus in 26.3 per cent and leg flexion in 0.8 per cent of trials. Second session, 96 trials: Head wagging in 27.1 per cent, and leg raising, in 41.7 per cent of trials.

November 21: First session, 30 trials: Head wagging in response to conditioned stimulus in none, whereas leg raising occurred in 96.7 per cent of trials. Most of responses occurred after eighth to tenth stroke of comb. Unconditioned stimulus now omitted (extinction). During next 30 trials, head wagging appeared in 23.3 per cent and leg raising in 6.7 per cent of trials in response to conditioned stimulus. Unconditioned stimulus now given after each conditioned stimulus (reenforcement). During next 30 trials, head wagging occurred 23.3 per cent and conditional leg raising 80 per cent of time in response to conditioned stimulus.

Nov. 25, 1947 to Feb. 20, 1948: Attempt to Produce Time Conditioning (chart 2): Dog stimulated for twenty to thirty minutes every six hours with electrified wire brush, thereby eliciting intense excitement. Continuous twenty-four-hour records of circling activity obtained prior to beginning of procedure and at intervals of two to three days during study. Although total circling activity and general irritability increased during study, such activity showed no consistent relation to hour during which animal was customarily stimulated (chart 2).

March 1: When removed from circular pen and placed in laboratory, dog collided with tables and other objects. When placed in corner, dog pushed head against wall for few minutes, then backed away and extricated self. Tactile and proprioceptive placing reactions of forelegs absent. Hopping reactions fairly good on left and poor on right. Abdomen appeared distended. Paracentesis yielded 1,200 cc. of light pink–yellow fluid.

March 9: Animal's general condition good except for recurrent ascites.

Attempt to Produce Visual-Motor Conditioning: Conditioned stimulus (electric light turned on before dog for five seconds), followed immediately by unconditioned stimulus (faradic shock to left hindleg); 232 trials. No conditioned response.

March 10: Same procedure continued; 357 trials. No conditioned response.

March 11: Same procedure; total of 980 trials since March 9. No evidence of conditioned response.

March 15 to April 13: Study of morphine addiction.

April 25: Dog died about noon. Complete autopsy. Cause of death apparently aspiration of stomach contents after vomiting.

Pathologic and Anatomic Study.—Gross and microscopic examinations of all tissues, except the brain, revealed the following abnormalities: massive necrosis

(atrophy) of liver; fatty degeneration of liver; extensive vacuolation of liver cells, probably glycogenic; pulmonary edema; lobular pneumonia; pulmonary emphysema; cloudy swelling of myocardium; vacuolation of spleen; moderate degeneration of epithelium lining the convoluted tubules of the kidneys.

Gross Description of Brain: The brain was covered for the greater part with an extremely thickened membrane composed of dura and subjacent leptomeninges. This tissue was pale and firm and was adherent to the underlying brain tissue. The cerebellum, medulla and pons appeared normal. The remaining brain structures were covered with the membrane described. Multiple coronal sections were made through the brain at intervals of approximately 3 mm. The first four sections through the frontal region did not reveal any remaining brain tissue. These sections were apparently composed entirely of thickened membrane. In

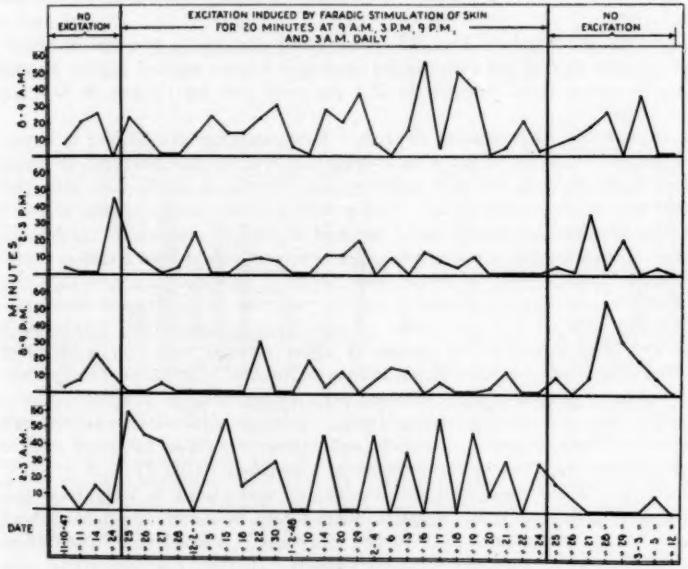

Chart 2.—Spontaneous preexcitation circling activity (dog 66).

the fifth section there was a small area of cerebral tissue, about 1 by 0.5 cm., the topographic relation of which could not be identified with certainty and which could only be determined by microscopic study. The subsequent sections revealed remnants of the basal ganglia, the third ventricle and, partially, the lateral ventricle. There was no evidence of the presence of the white and gray matter of the cortex. The next sections revealed an extremely distended aqueduct in the midbrain. The remaining sections showed normal-appearing midbrain, cerebellum, medulla and fourth ventricle.

Microscopic Study of Brain: The caudate nucleus was well preserved. Rostrally the lateral portions of this nucleus had been injured by the operation. The putamen was well preserved; the lateral portions had been injured by operation. The globus pallidus was well preserved. Operative injury was negligible. Practically complete removal of the cortex had been effected. The olfactory cortex

with the median bundle of the forebrain was intact on both sides. The lateral portions of this cortex had been removed. However, all cortex was removed lateral to the anterior rhinal sulcus. The piriform lobe was present on both sides. Complete neocortical removal was insured by destruction of the rhinal fissure throughout its extent. The corpus callosum was absent in most of the brain. Where it remained, few fibers could be seen in it. The ventricles were extensively dilated. This dilatation probably did not affect the remaining neural tissue. The amygdaloid nuclei were present throughout the brain. They were distorted by the ventricular dilatation but had probably remained functional for the most part. However, it should be noted that definite gliosis was seen in the anterior commissure, which might indicate injury to the nuclei amygdalae. The hippocampus had been removed entirely except for the most caudal portion of one side. The thalamus showed generalized loss of cells with gliosis. The entire ventrolateral region had undergone heavy gliosis, with only a few scattered cells remaining. The nuclei of the midline were well preserved. The thalamus as a whole did not show prominent atrophy, as one would expect to see in an animal which had survived so extensive an operation for any great length of time. The hypothalamus was apparently normal. All the nuclei stood out prominently. The medial geniculate bodies showed striking, but not complete loss of cells with gliosis. The lateral geniculate bodies showed degenerative changes. The nuclei of the midbrain were normal. The pyramids and internal capsule exhibited heavy loss of fibers. This, however, was not complete, probably owing to the intact corpus stratum.

Dog 75.—Feb. 20, 1947: Left hemidecortication.

February 23: Dog swallowed food placed in oropharynx; up walking (circling) much of the time.

April 2: Double amalgam fillings placed in both lower canine teeth (pentobarbital sodium anesthesia).

April 8: Stimulation of nerve of the tooth pulp through double amalgam fillings with 60 cycle current. Pain thresholds: right, 0.7 volt; left, 1.2 volts. Response consisted in twitch of same side of lower lip and retraction of head.

April 11: Tooth pain reaction threshold: right, 0.6 volt; left, 1.0 volt.

April 21: Decortication completed by removal of right hemisphere.

April 22: Dog very restless; attempted to right self.

April 23: Animal circling to left; quieter.

April 24: Circling to left; dog showed violent rage when restrained. Tooth pain reaction threshold: right, 0.8 volt; left, 1.6 volts.

April 25: Dog swallowed food placed on tongue; lapped liquids when snout was thrust into bowl. Squatted to urinate like female dog. Tooth pain reaction threshold: right, 1.0 volt; left, 1.5 volts.

May 8: Female dog in heat placed in tub; decorticated dog showed no reaction.

June 2 to August 3: Study on methadone addiction.

October 6: Dog observed standing on hindlegs in circular pen with forepaws on edge of wall, as though attempting to climb out.

October 7: Dog still squatted to urinate; no reaction to female dog in heat.

October 14: Attempt at Auditory-Motor Conditioning: Conditioned stimulus (pure tone of 500 cycles per second for six seconds), followed immediately by unconditioned stimulus (shock to left hindleg), evoking unconditioned response (flexion of the leg and weak bark). Twenty trials of conditioned stimulus, followed by unconditioned stimulus: no conditioned response.

October 15: Same procedure; 300 trials: no conditioned response.

October 16: Same procedure; 497 trials: no conditioned response.

October 17: Same procedure; 203 trials; no conditioned response; terminal restlessness.

October 20: Attempt to Produce Tactile-Motor Conditioned Response (fig. 1): Unconditioned stimulus, faradic shock to left hindleg: unconditioned response, flexion of left hindleg and vocalization. Conditioned stimulus, 10 strokes of comb along middle of lower back, 144 trials: no conditioned response.

October 21: Same procedure; 213 trials: no conditioned response.

October 22: Same procedure; 256 trials, in two sessions: Beginning with trial 604, conditioned leg raising (conditioned response) appeared 21.1 per cent of time during remainder of session.

October 23: Same procedure. First session, 96 trials: 87.5 per cent conditioned responses.

Second session, 48 trials: 54.2 per cent conditioned responses.

October 24: First session, 48 trials: 62.5 per cent conditioned responses.

Second session, 64 trials: 71.9 per cent conditioned responses.

Third session, 50 trials, omitted unconditioned stimulus (extinction): conditioned response, 22.0 per cent.

Fourth session, 50 trials, unconditioned stimulus omitted (extinction continued): conditioned response, 2.0 per cent.

Fifth session, 50 trials, unconditioned stimulus given after each conditioned stimulus (reenforcement): conditioned response, 56.0 per cent; most responses between eighth and tenth stroke of comb.

November 5: Attempt to Produce Auditory-Motor Avoidance Conditioning: Same procedure as on October 14, except avoidance made possible by lifting leg off grid.

First session, 40 trials: no conditioned response.

Second session, 60 trials: no conditioned response.

November 6: Same procedure; 74 trials: no conditioned response.

November 7: First session, 120 trials: no conditioned response.

Second session, 50 trials: no conditioned response.

November 10: First session, 86 trials: no conditioned response.

Second session, 96 trials: no conditioned response.

November 12: First session, 131 trials: no conditioned response.

Second session, 99 trials: no conditioned response.

November 13: First session, 59 trials: no conditioned response.

Second session, 144 trials: no conditioned response.

November 14: First session, 53 trials (total, 1,030 trials): no conditioned response.

December 2: Fistula in left parotid gland made with the use of pentobarbital sodium anesthesia.

December 4: Dog removed from circular pen and allowed free in laboratory; collided with objects, then tried to walk over them; occasionally seized blanket on floor and shook head vigorously from side to side. Methylrosaniline chloride, 1 per cent, placed in mouth, evoked profuse salivation, head shaking and rage. Fistula patent.

Jan. 12, 1948: Salivation from fistula when dog was picked up for feeding in forenoon; no increase in salivation when animal was placed in feeding box; feeding omitted; animal very restless and irritable, salivating profusely. Attempts made to extinguish tactile salivatory response by picking up dog frequently without feeding; no change in response.

January 13: Feeding still deferred. Dog more restless and irritable; salivated before being picked up. Attempt at extinction continued; no change. After feeding, dog showed little or no salivation, either spontaneously or when picked up.

January 14: Salivating before feeding. Extinction of tactile salivatory response again attempted; no change. Salivation greatly diminished after feeding.

February 12: Attempt to produce conditional salivation to injections of morphine. Each morning, before feeding (feeding deferred to afternoon), dog placed in light harness in conditioned reflex chamber for twenty minutes; then morphine, 5 mg. per kilogram of body weight, injected subcutaneously. Within three minutes after injection, salivation from fistula and mouth observed; then animal vomited, and this was followed by sedation. Procedure repeated daily. Occasional injections of saline solution given as additional conditioned stimulus.

February 20: Dog very irritable in harness and salivated before injection of morphine. Tolerance to emetic and sedative effects evident.

February 21 to March 22: No evidence of conditioned salivation. Dog extremely excited, struggled, exhibited sham rage and salivated profusely (before injection of morphine). Salivation seemed part of general irritability attendant on morphine addiction. Preinjection salivation very different from that of control, normal dog, which stood quietly and salivated profusely before injection during morphine addiction. Salivation in decorticated dog ceased when rage terminated.

March 23: Relation of Salivation to Rage: Dog replaced in circular pen, salivating slightly from fistula. Intense excitement induced by stimulating skin with electrified wire brush; excitement accompanied with profuse salivation. After excitement subsided, salivation diminished. Procedure repeated, with similar results.

March 23 to April 30: Study of Morphine Addiction.

April 30: Dog died during period of withdrawal (aspiration of vomitus). Complete autopsy.

Pathologic and Anatomic Study.—Gross and microscopic examinations of all tissues, except the brain, revealed the following abnormalities: Pulmonary emphysema; pulmonary atelectasis; pulmonary anthracosis, slight; small vacuoles in the alveolar tissue, possibly due to lipid material; acute interstitial myocarditis with small petechial hemorrhages into myocardium; periarteriolosclerosis in myocardium; cloudy swelling of myocardium; fatty degeneration of liver; groups of cells containing vacuoles, probably glycogenic; zones of reticuloendothelial proliferation in spleen; vacuolation of epithelium lining the convoluted tubules in the kidneys, probably due to glycogen.

Gross Description of Brain: The brain was entirely covered by a thick membrane except the cerebellum, medulla and midbrain. This membrane measured about 3 cm. in thickness and was composed of very firm connective tissue. Serial sections of the brain made coronally at about 3 mm. intervals revealed complete absence of cortical tissue, distention of the lateral ventricles and preservation of the basal ganglia. Sections through the pons, midbrain and cerebellum were normal in appearance.

Microscopic Study of Brain: By far the greater part of the caudate nucleus was destroyed on both sides. Only a few small nuclear portions remained. The greater part of the putamen was destroyed on both sides, a small portion remaining. However, relatively more of the putamen than of the caudate nucleus remained. The globus pallidus was injured in part. Many cells remained, but the lateral regions were destroyed. This structure was injured less than the caudate nucleus and the putamen. Complete removal of the neocortex had been

effected. Small portions of the olfactory cortex and the amygdaloid nuclei remained. Removal of the olfactory portion was more extensive than in dog 66. The over-all operative picture was very similar to that of dog 66. Most of the hippocampus was intact. The thalamus showed generalized cellular loss with gliosis. Heavy gliosis, with only a few scattered cells remaining, characterized the ventrolateral portion of the thalamus. Atrophy and distortion of the nuclei had occurred. Many normal cells remained in the nuclei of the midline. A much more detailed reconstruction would be necessary to determine which nuclei were affected and which were not. The hypothalamus was apparently normal. All the nuclei were prominent. The medial geniculate bodies showed definite loss of cells with gliosis. As in dog 66, the cell loss was not complete. Degenerative changes were seen in parts of the lateral geniculate bodies. All the nuclei of the midbrain were normal. The pyramids and internal capsule showed heavy loss of fibers. Only a very few myelinated fibers could be seen. The internal capsule was injured laterally on one side in the region of the caudate part of the globus pallidus.

Additional Notes.—Both preparations, during the first few days after decortication was completed, swallowed food only when it was placed in the oropharynx. Later, swallowing was accomplished when food was merely placed on the tongue. Neither decorticated dog showed any evidence of recognizing food, food bowls or the box in which it was placed for feeding. If the snout was thrust into a bowl of food, the animal ate until the bottom of the bowl was reached. It would continue to lick at the same spot, even though no food was thus obtained. At no time did either animal proceed to lick adjacent portions of the bowl which still were full of food. Both dogs exhibited rage when picked up and handled in preparation for feeding, even though the same attendant fed them daily. In the early months after decortication, only progression movements were exhibited. Later, both animals frequently backed away when seized by the loose skin on the back of the neck. The only "emotions" which the animals exhibited were those of rage and fear. During the period of withdrawal of morphine or methadone, to which the animals were addicted, both decorticated dogs exhibited sustained biting, gnawing and grubbing with the nose and mouth on the floor of the circular pen, usually in the corner at the junction of floor and wall. In dog 75 this activity was so intense that pressure necrosis of portions of the upper lip developed. This peculiar behavior was seen only during the period of withdrawal of the drug and lasted several days.

COMMENT

Pavlov [5] stated the belief that conditioning was not possible in the absence of cerebral cortex. Subsequently, several reports to the contrary appeared in the literature.[6] However, the problem remained unsettled because the removal of neocortex in such preparations was not complete. Culler and Mettler [7] were able to demonstrate only generalized con-

5. Pavlov, I. P.: Conditioned Reflexes, translated and edited by G. V. Anrep, London, Oxford University Press, 1927, pp. 430.

6. Hilgard, E. R., and Marquis, D. G.: Conditioning and Learning, New York, D. Appleton-Century Company, Inc., 1940, pp. 429. Lebedinskaia, S. I., and Rosenthal, J. S.: Reactions of a Dog After Removal of the Cerebral Hemispheres, Brain **58**:412-419, 1935.

7. Culler, E., and Mettler, F. A.: Conditioned Behavior in a Decorticated Dog, J. Comp. Psychol. **18**:291-303, 1934.

ditioned responses in a completely decorticated dog. Recently, however, Bromiley [8] reported the development of discrete conditioned motor responses, and even differentiation of auditory stimuli, in a long-surviving dog in which all neocortex had been removed except for a small fragment of gyrus proreous.

The observations presented in this paper indicate that complete removal of neocortex results in a very marked impairment of acquired adaptation. However, the effects are not "all or none" but, rather, changes of varying degree. Thus, in the 2 decorticated animals, reflex responses to sound ("startle" or "orienting" reactions), light (closure of the lids, contraction of pupils) and tactile stimuli (licking reflexes, righting) were readily elicited. However, neither auditory nor visual motor conditioning could be produced, whereas an apparent conditioned motor response to tactile stimulation was elicited only after prolonged effort.

Reactions suggestive of a crude form of conditioning were observed when the preparations were excited, as, for example, when hungry or when restrained, toward the end of a conditioning session, during morphine addiction or after direct stimulation of the skin with an electrically charged wire brush. Under such conditions, a generalized response, including motor activity, barking and salivating, would frequently follow any stimulus, especially a tactile one.

The behavior of the preparations in other than formal conditioning procedures also showed evidence of uneven, crude adaptations. Thus, both animals were better able to extricate themselves from corners several months after decortication than earlier. During the early period after completion of decortication, the preparations circled about in the pen by pressing one side to the wall. Later, they circled close to the wall, but without actually making contact with it. At first, the spontaneous activity of the preparations was limited to circling, lying down, sleeping, defecating and urinating. Later, they were frequently observed to paw the walls of the tub, and occasionally they placed both forelegs on the edge of the wall as though attempting to climb or jump out. During the last few months of its postoperative existence, dog 75 occasionally seized the blanket on the floor with his teeth and shook his head vigorously, as though biting off part of a carcass. In evaluation of such patterns of activity as these, it is difficult to distinguish between "learned" adaptation and emergence of reflex patterns after decortication by a process similar to that of recovery from "spinal shock" after transection of the spinal cord.

On the other hand, neither preparation ever showed any evidence of recognition of the attendant who fed and cleaned it daily, or of the

8. Bromiley, R. B.: Conditioned Responses in a Dog After Removal of Neocortex, J. Comp. & Physiol. Psychol. **41**:102-110 (June) 1948.

open box in which it was placed for feeding. The reaction to handling was always one of sham rage. Similarly, the animal showed no reaction to the needle prick during the administration of the daily clysis of saline solution, even though after about 50 cc. of isotonic sodium chloride solution had been injected the preparation would always react with vigorous rage.

Of interest, also, are incidental observations not directly related to the main problem. One was the occurrence of an apparently unconditioned tactile salivatory response when the dog was hungry. When first observed, it was thought to be a conditioned response, but it could not be extinguished by repeated tactile stimulation without feeding. The response did not occur, or was greatly reduced, after feeding. In this respect, it differed from the unconditioned salivatory response to food which Gantt [9] has shown to be independent of "motivation." Another was the observation that after decortication dog 75, a mature male, always exhibited the female postural pattern on urination. This animal never showed any reaction to a female dog in heat, but it should be noted that the olfactory tracts had been sectioned. In both animals the reaction to electrical stimulation of a canine tooth was unaltered by complete decortication, although the threshold was slightly elevated.

A study of the microscopic picture in the 2 decorticate dogs fails to provide an anatomic explanation of the differences between the effectiveness of tactile and that of other stimuli in establishing adaptive responses. The ventrolateral nuclei of the thalamus were replaced by glia as completely as, or more than, were the medial or lateral geniculate bodies. It must be assumed, therefore, that other portions of the remaining brain were utilized in the development of conditioned tactile stimuli.

The "conditioned" responses to tactile stimuli seen in the 2 decorticate dogs were of two types. In dog 66, head wagging in response to conditioned tactile stimuli was first observed in October 1946 during attempts to establish conditioned flexation of the leg. The response was inconstant, and the effects of extinction and reenforcement procedures were equivocal. It is possible that here, too, head wagging was part of a generalized unconditioned orienting reflex which was intensified by repeated stimulation. The discrete leg-raising response to conditioned tactile stimuli resembled more definitely an acquired adaptation or conditioned response in that it became more stable with each successive training session and was readily extinguished or reenforced. The effectiveness of this type of tactile stimulus (stroke of a comb on the back) in evoking a conditioned motor response may perhaps be explained on the basis of facilitation of the scratch reflex by prior elicitation of the flexor reflex. The prolonged internuncial activity characteristic of the latter may result in an enduring intensification of "central excitatory

9. Gantt, W. H.: Effect of Satiation on the Intensity of the Conditional and Unconditional Salivary Secretion, abstracted, Federation Proc. 7:40, 1948.

state" in the vicinity of the motoneuron pool supplying the hindlimb and thus facilitate other responses which utilize the same motoneurons. In keeping with such an explanation is the fact that most of the "conditioned" leg-raising responses to the tactile stimuli occurred on the eighth to the tenth stroke of the comb. This suggests summation of the excitatory effects of the tactile stimuli with those remaining from the last previous flexor response to faradic shock of the hindleg (the unconditioned stimulus). Whether such responses should be called conditioned at all is debatable. However, they possess many of the characteristics of conditioned responses and may represent a very primitive type of "learning" which merits further study in relation to the general theory of conditioning.

SUMMARY AND CONCLUSIONS

The postoperative life histories of 2 decorticated dogs, one surviving nineteen and the other twelve months, are presented. Anatomic studies of the brains in these animals revealed no traces of remaining neocortex.

The dogs showed spontaneous changes in the direction of better adaptation with increasing postoperative age in connection with swallowing food, avoiding the walls of their circular pens, extricating themselves from corners, escaping from the grasp of the attendant and attempting to escape from the pen. On the other hand, the preparations showed no recognition of food, food receptacles, the attendant who always fed them or the needle prick which always preceded clyses with saline solution and which regularly evoked rage.

Formal attempts to produce conditioned motor responses to visual and auditory stimuli, either by the classic pavlovian method or by avoidance technics, were not successful. Discrete conditioned motor responses to tactile stimuli were established after prolonged efforts. During attempts to produce conditioned salivation associated with injections of morphine, salivation was observed only as part of a generalized rage response before injection of the drug. Attempts to produce time conditioning of increased motor activity were not successful.

An unconditioned tactile salivatory response was observed which was intensified by hunger and diminished by feeding. After complete decortication, one of the dogs (an adult male) reverted to the female posture during urination. Decortication did not alter the pattern of the reaction of the dogs to electrical stimulation of the pulp nerves of teeth; the threshold of such reactions appeared to become elevated slightly after the operation.

These observations are discussed with reference to the problem of adaptation and conditioning.

ROLE OF SOMESTHETIC STIMULI IN THE DEVELOPMENT OF SEXUAL EXCITATION IN MAN

A Preliminary Paper

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THE IMMEDIATE goal of the sexual urge in the male is the discharge of seminal fluid, the ejaculation.[1] It is effected through reflex mechanisms. However, before it occurs there is a period of varying extent during which he perceives a series of sensations and increased excitability in both the somatic and the psychologic sphere. The somatic manifestations are mediated through the autonomic and central nervous systems and are present as penile erection, increased heart rate, elevated blood pressure, deepened respiration and flushed facies. The psychologic reactions are experienced as specific pleasure and accompanying specific displeasure, or tension. As the tension becomes more acute, the degree of excitation increases. It is a unique feeling of pleasure, as well as prevailing discomfort, which demands relief in the ejaculation.

This combination of somatic and psychologic reactions will henceforth be referred to as "sexual excitation."

In the normal male the initiation of sexual excitation can be brought about in one of three ways: (1) mental stimulation, (2) activity of the endocrine glands and (3) somesthetic stimuli, mostly coming from the sexual organs. On the other hand, one of the same factors can inhibit sexual excitation. The mental [2] and endocrine elements [3] have been studied by others in this regard. The role of a complete somesthetic disturbance, however, has not yet been ascertained. It was felt that this important subject deserved investigation. This paper is the result of such a study.

MATERIAL

In seeking to evaluate the effect of disturbed stimuli from the sexual organs on sexual excitation (a mentally dominated activity), it was necessary to observe patients whose somesthetic tracts to the brain were cut off. In addition, this dis-

From the Neurological Institute of New York.

1. Federn, P.: Personal communication to the author.

2. Hirsch, E. W.: Psychic Impotence, Illinois M. J. **74**:279-283, 1938.

3. Carmichael, H.; Noonan, W. J., and Kenyan, A. T.: The Effects of Testosterone Propionate in Impotence, Am. J. Psychiat. **97**:919-943, 1941.

ability was not to interfere with the proper functioning of the endocrine or the mental system. The one group of subjects who satisfied these criteria were paraplegic patients with clinically transected spinal cords. Patients who had paraplegia due to poliomyelitis but in whom the sensory modalities were intact were used as controls.

Nineteen patients with transection of the spinal cord were examined. Twelve appeared to have complete transections, since there was motor paralysis of the lower extremities, paraplegia in flexion or flaccid paralysis, absence of sensation below the level of injury and absence of bowel and bladder control. Seven patients had partial transections. In these patients sensations of various intensities were perceived below the site of injury, but motor paralysis was present.

All 19 patients were male. The ages varied from 19 to 42 years; most of the patients were in the late twenties.

Only 4 of the cases of "complete" transection will be reported in detail at this time. Two of the 4 patients studied were at the Neurological Institute of New York, and 2, friends of the aforementioned patients, were observed outside the hospital.

The case histories follow.

REPORT OF CASES

CASE 1.—The patient, a native white American aged 31, was graduated from public school and high school as an average student. His inclination was always toward sports, and he played semiprofessional basketball, soccer and baseball. He was well liked and had a fairly large circle of friends.

Puberty started at about 13 years of age. His first reollection of masturbation was at the age of 17. He felt that it was wrong and devoted more of his energies to athletics. However, he noticed that he masturbated in his sleep once every two or three weeks and achieved an ejaculation at such times. His dreams at those times were of caressing various girls of his acquaintance.

At the age of 19 he met his wife; he courted her for four years, until he married her, at the age of 23. In the interim he petted with her but did not have intercourse. After marriage he had sexual intercourse at least once every day for one month. His erections were normal throughout the act, and he always achieved an ejaculation. His wife was well satisfied with his potency, and they had orgasms simultaneously.

One month after his marriage (January 1942) he was inducted into the Army of the United States and was sent successively to four different camps in the states during a two year period. Four separate furloughs, amounting to over a month, were spent at home. Sexual relations with his wife were then frequent and satisfactory. After this he was sent overseas. He remained abstinent until he returned home, in December 1945.

His sexual life became routinized, and he had marital relations approximately twice a week. He and his wife derived great satisfaction therefrom.

In May 1947 a baby was born to his wife, and he was "very thrilled" at this event. Two months later, he fell from a height while engaged in his work and landed on his right shoulder and neck. He was unconscious for a few minutes and then recovered long enough to realize that he was paralyzed in all extremities. He lapsed back into unconsciousness for about four days. After this he improved partially, recovering the use of his upper extremities. There were paraplegia in flexion and "numbness from nipples to toes." He had lost bladder and bowel function. Reflex penile erections were present, but there were no sensations from the genitalia.

Three months after the injury, a laminectomy from the second to the sixth thoracic vertebra was performed. The patient was told that he had a severely crushed spinal cord.

He was first admitted to the Neurological Institute on Aug. 1, 1948, approximately one year after the injury. Physical examination revealed a pleasant-looking white man, who appeared to be of his stated age, 31 years. The upper part of his body was well developed and nourished, but his legs and thighs were thin. The muscles were atrophic. There were bilateral foot drop and paraplegia in flexion. A clearcut sensory level was present at the sixth thoracic dermatome, with complete loss of all modalities (pain, touch, temperature, vibration and position senses). He was not in control of the bladder or bowel, requiring tidal drainage for the former (hypotonic bladder) and enemas for the latter.

The patient was disturbed by severe flexor spasms and mass reflexes. Curare and mephenesin (myanesin®) were ineffective in coping with the spasms, and a subarachnoid block was therefore performed on Oct. 8, 1948, 15 cc. of absolute alcohol being instilled. This caused complete flaccid paralysis of the legs, disappearance of the spasms and loss of erections. He felt much cheered as a result of the improvement in his spasms. The tidal drainage was removed, and the patient was taught to catheterize himself. He is now being fitted with braces preparatory to his discharge home.

His dreams, which have occurred about once every four months since his accident, are concerned chiefly with walking. He sees himself going to a ball game or to a movie with his wife or taking the baby for a walk. He has clear body feeling impressions of himself walking.

On occasion, he dreams of himself about to mount his wife. Both he and she are nude. He visualizes himself moving his legs but does not conjure up a picture of his penis, either in the flaccid or in the erect state. At the moment when he mounts his wife he awakens.

During a stay at home from the hospital, he realized that the body of his wife did not excite him. He would touch her, but he was sexually unmoved. In the hospital he never has erotic feelings toward any of the nurses. He never experiences penile sensations and has not had any erections or ejaculations since the arachnoid block.

The activities which were wont to "thrill" him in the past have lost a great deal of their allure, and there has been a general sagging in all interests, although his morale is on a high level.

The patient described one of his dreams as follows:

"I was at work in a building. I don't know what kind of work. I was talking to a cousin. I asked him to go to a hall and play basketball. We went over there. There were seven or eight, or maybe ten others. I enjoyed playing ball. I did not get any sexual feeling.

"It reminds me of my past when I played ball myself. All my dreams seem to be of the past,[4] but I have no sex dreams. It just ain't there any more, I guess. Once in a while I think of going home and about what I can do—what the household is going to look like and all that."

The patient was asked if he tried to picture himself in sexual situations, and he replied, "It doesn't come about, so I don't bother."

Case 2.—An American white youth aged 19, single, in April 1948, while working as a carpenter's helper trimming a house, fell from a ladder 15 feet (4.5 meters)

4. There is no regression of the ego to an earlier age—simply a dream of once cherished activities.

above the ground. He had hit his finger, become "stunned" and then lost his balance and fallen. He did not know how he landed. He stated the belief that he lost consciousness for a "few seconds." There was no bleeding from any orifice. Immediately after the injury he was unable to move his legs and noted numbness of the lower extremities and the body up to the waist. He was taken to a hospital, where a compression fracture of the bodies of the seventh and eighth thoracic vertebrae was found. Examination at that time disclosed "complete paraplegia." With the patient under ether anesthesia, hyperextension of the spine was effected, and a cast was applied.

The numbness and inability to move his legs were unaffected. He noticed, however, that his legs would occasionally "jump or jerk." His loss of urinary control necessitated the insertion of an indwelling catheter and tidal drainage. A number of decubitus ulcers developed, and the patient was transferred to the Neurological Institute of New York on July 23, approximately nine weeks after the accident.

Physical examination revealed numerous decubitus ulcers of the buttocks and sacral and lumbar areas. There were flaccid paraplegia and areflexia of both lower extremities except for a slight reaction in the hamstring muscles, absence of pathologic reflexes and a sensory level at the eighth thoracic dermatome, below which all modalities, such as pain, touch, temperature, vibration and position senses, were lost.

A roentgenogram of the spine showed an old compression fracture of the eighth and ninth thoracic vertebrae, with good alinement and slight narrowing of the intervertebral spaces.

On September 25 a periurethral abscess formed. The "scrotal sac and testes were normal." An incision was made and drainage instituted, and the condition healed.

A spinal puncture revealed 252 mg. of protein per hundred cubic centimeters and 3 white blood cells per cubic millimeter. A myelographic study was performed. Study of the subarachnoid space as high as the midthoracic region showed complete obstruction to the flow of the opaque medium at the upper margin of the ninth thoracic vertebra. Laminectomy of the ninth and tenth thoracic vertebrae was therefore done and showed an intact cord. There was no appreciable change in the patient's condition after the decompression.

The patient in his earlier years had attended public school and high school and was graduated as an average student. He was friendly and outgoing, with a fairly large circle of friends. His chief interests were swimming, fishing and hiking.

His first recollection of masturbation was at the age of 12. He practiced this once every two days for about two years, and then on the average of once a week. His sexual phantasies at such times were of girls whom he knew. He had never had sexual intercourse.

His dreams since the accident, which are relatively infrequent, picture him as able to walk again. On one occasion he dreamt of walking with a nurse and kissing her. It was at this point that he wakened. He has frequent erections (reflex priapism) but no penile sensation. He does not experience any sexual excitement and never has any erotic thoughts toward the nurses who bathe and minister to him. Rarely, he tries to test himself by embracing a nurse but is disappointed in his own lack of response. He stated, "If they stood nude in front of me—the whole bunch of them—it wouldn't bother me."

At no time has he been able to visualize himself with an erection, although he has tried to do so. He has maintained an interest in sports and reading, but the

keen enthusiasm which he had before for these activities has been considerably dulled.

An endocrinologic consultant reported, "No evidence of glandular failure." The urinary excretion of 17-ketosteroids was normal.

The next 2 patients to be reported on had been rehabilitated years before and were not confined to the hospital at the time of their interviews.

CASE 3.—The patient, a white married man aged 39, was injured by shrapnel in 1944, while in the armed forces, and sustained "complete" transection of the cord with a definite sensory level at the fourth thoracic dermatome.

The past history revealed him to be an extremely outgoing and popular person, who always considered himself well adjusted. He was married at the age of 26 and had a child as the result of that union. Both he and his wife had strong sexual drives and enjoyed sex relations three or four times a week. His erections were satisfactory, and his orgasms were "powerful," as were those of his wife.

After the injury, he lost sensation in his genitalia and has since no real desire for intercourse. On one occasion he masturbated to test the extent of his feeling, but he was disappointed because he did not know that he "was doing it and couldn't feel anything." He has erections, which vary from a few seconds to about a half-hour, but he does not have any ejaculations. During intercourse, which is usually initiated by his wife, he makes a point of keeping the light on in the room. He does not perceive any sexual excitation but derives a great deal of satisfaction from the fact that he is affording pleasure to his wife.

His dreams are infrequent, and the contents are quickly forgotten on awakening.

For several years after the injury, he noted a definite sagging of interest in life and events about him. However, he "willed" himself to participate in activities and now has a much richer schedule than he had when he was well.

CASE 4.—The patient, a white married man aged 41, fell through a hatchway in the hull of a ship in 1944, while in service, and sustained a "complete" transection of the cord at the tenth thoracic level. The anamnesis from early childhood showed that he had had a normal development. He was successful in business, married well, had a child and enjoyed a good relationship with his wife. Prior to the injury, he had strong erections and intercourse three to four times a week that was satisfactory to both his wife and him. When the frequency of the act was disturbed from time to time, he would have "sexual dreams."

Immediately after the accident, the sexual status changed abruptly. He could not have any erections or ejactulations, did not have sexual thoughts and felt no libidinous drives. He gave up trying to have sexual relations and said, "I have no need for sex."

He has remained happy in his home life because of the devotion of his wife and child and has reestablished his interest in events around him more than has any other patient interviewed.

His disposition is calm and pleasant even under stress, and he does not show any significant outbursts of temper. There is no evidence on considerable probing to indicate a regression to a pregenital type of sexuality, such as voyeurism, exhibitionism, masochism or sadism. He is active in his business and gets around by himself in a wheelchair or employs braces and canes for support and locomotion.

He occasionally has walking dreams, but none other of a more frankly sexual nature.

COMMENT

In all the 4 cases presented, there was evidence of an injury to the spinal cord in the thoracic area. The levels were the sixth, eighth, fourth and tenth thoracic, respectively. In the first case, the patient was paralyzed in all extremities immediately after the accident, indicating a lesion in the cervical portion of the cord. His condition improved over a period of time, however, and he regained the use of his upper extremities. Examination now reveals the level to be at the sixth thoracic segment.

Clinically, in every instance, the lesion appears to be a complete transection of the cord. Sensory modalities, i. e., pain, touch, temperature, position and vibration senses, are not perceived below the site of injury. There is absence of bowel and bladder control and of voluntary motor power in the lower extremities.

Flexor spasms and mass reflexes were noted in all cases. The former reflex resembles a withdrawal, or defense, movement elicited by stimuli applied to the skin of the foot. Frequently it is produced spontaneously by a change in the patient's position in bed. It is a forceful and well sustained involuntary muscular contraction in the flexor muscles of the legs and abdomen. Such contraction (flexor spasms) and the synchronous contractions of many different groups of muscles are called the mass reflex. This is evidence of unchecked activity of the isolated portion of the spinal cord. The first patient was so disturbed by these often repeated mass reflexes that he was given a subarachnoid alcohol block. This greatly alleviated the condition, but the patient lost his reflex priapism as a result.

Another expression of automaticity is the ejaculatory reflex. It consists essentially of priapism and seminal emission, which may be elicited on the slightest stimulation of the glans penis. One patient (case 2) had an erection whenever any part of his penis was touched preparatory to changing an indwelling catheter. He experienced no sexual feelings at such times and felt no sensation whatever from the manipulation. He was operated on because of myelographic evidence of impingement of the ninth thoracic vertebra on the spinal cord. It was expected, in view of the severity of the injury, the duration of pressure of bone on the tissue and the extensive symptoms, that there would be definite changes in the cord. However, the cord was intact and appeared grossly normal. This brings up for consideration Grinker's [5] statement "that there is no clinical means of deciding whether

5. Grinker, R.: Neurology, Springfield, Ill., Charles C Thomas, Publisher, 1934.

a given symptom, indicative of complete loss of function, is due to complete anatomical severance of its pathway or to a physiological block of its function."

The criteria for the diagnosis of complete transection have undergone modifications since the formation of Bastian's [6] law, in 1882. At this time it was postulated that there had to be absolute anesthesia to all forms of stimuli and flaccid paraplegia, with loss of all reflexes and all visceral reactions below the site of the lesion. As a result of his experiences in World War I, Riddoch [7] stated that this was not so. He claimed, that here is a stage of flaccidity, then a stage of reflex activity, in which the bladder and rectum may act automatically and the muscle tonus may improve, and, finally, a stage of gradual failure of all reflex activity. The current universal concept is that after the initial "spinal shock," with its complete flaccid paralysis, tonus reappears and "paraplegia in flexion" develops. Merritt, and associates [8] in their recent book, extended these observations and stated:

It must be borne in mind, however, that occasional poorly sustained extensor spasms even of a bilateral type do occur in cases of complete cord transections.

The diagnosis of a complete, as against incomplete, transection of the cord was made in accordance with the criteria already indicated. In addition, an inquiry was made as to the patient's subjective reaction during sexual activity. For example, in 1 case, not described in detail, the condition could have passed for a complete transection, since the patient had total sensory anesthesia (loss of pain, touch, temperature, vibration and position sense) below the lesion, which was located in the middorsal area. He had motor paralysis of both legs, lack of bowel and bladder control and no voluntary erections. He felt no sensation in the penis but could have an erection when this member was handled (reflex priapism). However, he did experience a definite physical pleasurable feeling locally when he had an orgasm during intercourse, albeit the "charge" he derived was greatly reduced from that which he had prior to the accident. The case was classified as one of incomplete transection of the cord.

In the series reported, 3 patients were injured as the result of a fall. One fell from a height of 15 feet; a second fell from the top of a freight train to the ground, and a third, sustained his injury while in

6. Bastian, H. C., cited by Grinker.[5]

7. Riddoch, G.: The Reflex Functions of the Completely Divided Spinal Cord in Man Compared to Those Associated with Less Severe Lesions, Brain **40**:264, 1917.

8. Merritt, H. H.; Mettler, F. A., and Putnam, T. J.: Fundamentals of Clinical Neurology, Philadelphia, The Blakiston Company, 1947.

the service of the United States Navy, crashing through a hatchway in the hull of a ship. The fourth patient, also injured in service, was hit by a shell fragment.

Three of these patients were married. Three had had children prior to their injury. The fourth, aged 19, was unmarried. Not one of these patients has had any conscious feelings of sexual excitement or sexual desire since the injury. The individual periods have ranged from nineteen months to five years.

Two patients are still able to have erections, but these are reflex priapisms unaccompanied with any sensation. They can be induced merely by turning in bed, or they arise spontaneously without the patient's being aware of it. On occasion, handling the organ may cause a reflex erection. The nature and duration of these erections are varied. They may last from seconds to hours, and under constant stimuli may remain indefinitely. A third patient (case 1) had had erections, but these were abolished by a subarachnoid block performed for relief of disturbing mass reflexes in the lower limbs. Three patients who had incomplete transections similarly lost their erections after this procedure.

In the absence of sexual excitation, it is obvious that there is a defect in the interrelations of the three factors necessary to produce this emotional state (mental, endocrine and somesthetic stimuli). The situation, although admittedly oversimplified, may be likened to that of an electric circuit. The incandescent bulb represents the psyche; the wire containing the electricity, the endocrine system, and the switch, the spinal cord and the autonomic nervous system. The bulb may be perfect, and the wire may be intact, but if the switch does not make contact between the two, there will be no illumination of the bulb (sexual excitation).

It would appear from the facts observable in these cases that the switch (spinal cord and autonomic innervation) is defective and is responsible for the nonfunctioning of the unit. However, the other parts of the circuit must first be examined for possible contributory dysfunction (endocrine and psychic systems).[9]

ENDOCRINE SYSTEM

Diseases of various endocrine glands leading to loss of libido have been reported. Except for the past history of epididymitis in 2 cases in our series and its possible effect on the gonads, there is no evidence of involvement of the endocrine glands to account for the lack of sexual excitation. In the 2 cases mentioned, biopsy of the testes was not made.

9. In 2 cases of "complete" transections of the cord, not described, the patients stated that they did experience sexual excitation during the act of intercourse. These cases will be the subject of a future communication.

However, it is now the consensus that even a total loss of testicular function after puberty does not materially influence sexual feeling. Beach [10] stated:

> Men castrated in adulthood may continue to display strong penile reflexes for many years and often report frequent and satisfactory sexual intercourse. A few such individuals have been subjected to a hormonal analysis, and the resultant report reveals a castrate level of androgen concentrate.

Hirschfield [11] is convinced that despite a complete lack or a complete atrophy of the sexual glands there is considerable libido. Hamilton [12] reported on 2 patients who had been castrated for thirteen and eighteen years, respectively, and who had pronounced capacity for penile erections, observed during his repeated examinations.

> Statements as to the interest and ability in intercourse exhibited by one of these men who was married were corroborated by his wife. Low titers of urinary androgen and clinical and laboratory evidence of testicular insufficiency, including supranormal values for urinary gonadotropins, provide assurance that there was no considerable androgen secretion derived from extragonadal sources. . . . A marked capacity for penile erections may continue for many years subsequent to castration.

On the strength of the evidence aforecited, pursuance of the subject of testicular function has, therefore, no practical bearing on the problem under discussion—that of sexual excitation. However, there are further points in the status of the testes that are of academic interest. Horne and associates,[13] in their study of 18 cases of "complete" transections of the cord, consistently obtained specimens of semen containing spermatozoa in 11. Biopsies of the testes in 7 cases revealed conditions varying from complete atrophy of the spermatogenic cells to normal testicular tissue. The authors did not report the hormonal elaboration in either the atrophic or the normal testes.

In the present series, 1 of the patients with epididymitis had a normal urinary output of neutral 17-ketosteroids. A second patient, who did not show any testicular or epididymal involvement, also had a normal hormonal excretion. Of course, there were no symptoms in any case indicative of the climacteric, similar to the flushes, sweats or muscular weakness in the female menopause. There were likewise no changes in the secondary sexual characteristics, such as the voice, beard, distribution of hair or deposition of fat.

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10. Beach, F. A.: in Hoch, P. H., and Zubin, J.: Psychosexual Development in Health and Disease, New York, Grune & Stratton, Inc., 1949.

11. Hirschfeld, M.: Sexual Pathology, New York, Emerson Books, Inc., 1945.

12. Hamilton, J. B.: Demonstrated Ability of Penile Erection in Castrated Men with Markedly Low Titers of Urinary Androgen, Proc. Soc. Exper. Biol. & Med. **54**:309, 1943.

13. Horne, H. W.; Paull, David C., and Munro, D.: Fertility Studies in the Human Male with Traumatic Injuries of the Spinal Cord and Cauda Equina, New England J. Med. **239**:959, 1948.

PSYCHIC SPHERE

In the absence of any endocrine feature to account for the loss of sexual excitation, attention must now be focused on the next unit in the circuit which may be a causative factor—the psychic element.

It is well appreciated that a disturbance in this sphere, with an intact central nervous system, may result in loss of excitation. This apparent lack of sexual reaction may be due to strong repressive mechanisms. On the other hand, sexuality may be expressed in a disguised form, such as sadism or masochism, without the patient's being aware of its sexual nature.

It is necessary, therefore, to explore the devious avenues through which sexuality may be manifested. The main channels are (1) the patient's conscious attitude toward sex—his known desires, or lack of them—(2) sex feelings, as demonstrated in daydreams or dreams occurring during the course of sleep, and (3) regression to an earlier stage, permitting the utilization of partial instincts, scoptophilia, exhibitionism, etc., for gratification.

A number of persons, including nurses, neurosurgeons and neurologists, who have worked with paraplegic patients and whom I have interviewed, have the impression that the sexuality in this general group is heightened. They have been impressed by (*a*) the ready physical response of the patient to slight stimuli (erections), (*b*) the profusion of provocative pin-up girls around the ward and (*c*) the open discussion and jokes about sex which are flippantly indulged in by the patients.

These observations, although made by trained personnel, are necessarily superficial, and the deeper psychiatric probings into the underlying dynamics were not employed. It has already been seen that the reflex erections, although striking for their spontaneity and duration (in certain cases), are entirely devoid of the concomitant pleasurable and stimulating sensations that are present in the normal person., As for the discussions, it is a matter of common experience that "those who can, do!; those who can't, talk!"

These patients would like to act sexually as do their normal fellow men and continually test themselves in their ability to do so. The remarks of the 4 patients in the present small reported series is representative of the other patients interviewed, and no doubt reflect the reactions of the group as a whole.

One patient said, "When I stroke my wife, it's like touching wall plaster. I don't get a kick out of it." Another said, "I have no need for sex." A third placidly commented, "Before my accident, when I wanted relations, I had to have it, and I would manage to get it. Now, if I'm refused, I can read a book a minute later." The unmarried man constantly suggested that the physician should send a "pretty young

nurse" to him for sexual purposes so that he could judge his potency. When, in the course of their duties, the nurses did have contact with him in changing his pajamas, making his bed or massaging his back, he was entirely indifferent to their closeness. On occasion, he would slip his arm around a nurse's waist. There was no sexual excitement in his request or in his reactions.

One of the men in the group, not described, characterized the change with the following remarks, "Before, when I saw a woman boarding a bus and her dress went up, I would get the right reactions. Now I look and just think 'That's a nice leg'—it's all in the head."

A number of patients have been unfaithful to their wives in the hope that the next woman will be sufficiently stimulating to bring about the excitation which they no longer feel. This never occurs.

If one assumes, for the sake of discussion, that this diminution in sexual libido is due to suppression, then one of the most cogent reasons for its development is that the patient is unable to perform the sexual act and therefore does not wish to experience the resulting frustration. However, we have noted, to the contrary, that the majority of patients do have erections. These erections are strong. In some instances they can be sustained indefinitely, and yet there is no sexual feeling, no preceding pleasure and no gratification. Many patients, nevertheless, are very active sexually because they wish to test themselves and also to afford satisfaction to their love objects (wives, fiances, friends). It is important for them to feel that they are supplying a need.

On the other hand, the knowledge that sexual gratification cannot be achieved may conceivably diminish libido. One would then expect the person to avoid sexual activity because of frustration. The great amount of "fake" sexuality in which some of these patients indulge proves that they have learned to avoid painful humiliation. Nurses are often chosen as love objects because they appreciate the patient's predicament and are sympathetic to the "accidents" that are always occurring (to these patients).

It might be thought that the trauma, by causing many psychologic responses, could reawaken preexisting sexual difficulties. There is no evidence of such past disturbances in any of the cases described.

DAYDREAMS AND NIGHT DREAMS

Both daydreams and night dreams are mental phenomena which represent fulfilment, or attempted fulfilment, of dreams. The content of the day phantasies "is dictated by a very transparent motivation. They are scenes and events which gratify either the egoistic cravings of ambition or the thirst for power or the erotic desires of the subject. In young men ambition phantasies predominate—but the erotic requirement can often enough in men too be detected in the background. All

their heroic deeds and successes are really only intended to win the admiration and favor of women." [14]

The 4 patients in the series reported here were peculiarly deficient in such daydream activity. Other members of the group interviews also showed the same reaction.

All patients, whether they had a "complete" or a partial transection of the cord, admitted a definite change in their nocturnal dream life. The reported number of dreams was strikingly reduced.

One patient, after a subarachnoid alcohol block, lost his reflex erections, and the number of reported dreams became fewer. Two other patients, with incomplete transections, who had some degree of genital sensation, erections and dreams, were similarly given subarachnoid alcohol blocks for forceful flexor spasms. The spasms were eliminated, as were their erections. There was also diminution of reported dreams.

Sheldon and Bors [15] reported performing subarachnoid alcohol blocks on 24 patients with paraplegia. Twenty-two of this number lost their erections.

Out of 17 patients with sexual dreams before block, 6 underwent dream conversion after block. Five patients lost sexual dreams entirely.

It would thus appear that genital stimuli play a part in the formation of dreams It may still be that the sleep became deeper because the patient was less disturbed or that there was an equivalent number of dreams which were forgotten on arising.

All patients had dreams of walking. These dreams implied manifest wish fulfilment. Apparently, they have no problem to be solved. Yet, Freud found that most occupational and ambulatory dreams symbolically express the desire for sexual performance.

The dreams which are frankly sexual in content can be placed in two categories: (1) kissing dreams, not leading to intercourse or ejaculation, and (2) attempts at intercourse, the patient awakening before completion. The patient does not experience excitement in the role of either protagonist or observer. Not one of our patients had had an emission or an orgasm. This form of dreams does not differ from most dreams which accompany a nocturnal emission in normal persons. They contain the preparatory step toward intercourse, which is interrupted by the awakening. Usually there is no libidinous pleasure in these "shortened" dreams.

Bors [16] mentioned that a few of his patients had ejaculations and orgasms. These detailed reports have not yet been published.

14. Freud, S.: A General Introduction to Psychoanalysis, New York, Liveright Publishing Corporation, 1935.

15. Sheldon, C. H., and Bors, E.: Subarachnoid Alcohol Block in Paraplegia: Its Beneficial Effect on Mass Reflexes and Bladder Dysfunction, J. Neurosurg. **5**:385, 1948.

16. Bors, E.: Spinal Cord Injuries, United States Veterans Administration Technical Bulletin 10-503, Washington, D. C., Government Printing Office, 1948.

PERVERSIONS

Many paraplegic patients practice perversions, but they cannot be considered as perverts. They do not fall into the category of "persons with infantile instead of adult sexuality," whose genital orgasms are "blocked by some obstacle that is more or less overcome by the perverse act" (Fenichel[17]). These patients merely use their tongue or finger as unfailing phallic substitutes to supply satisfaction, although they themselves do not perceive any frank sexual drive or sexual excitation.

A case in point is that told personally by Dr. De Luca. One of his patients had performed cunnilingus on his partner. She then asked what she could do for him in return, and the reply was, "Nothing at all—just forget it."

REPRESSION

The possibility that repression of sexuality operates in these cases is a consideration. Unfortunately, the number of dreams are too few to determine this adequately. Neither hypnosis nor psychoanalysis was employed to solve this question.

PARAPLEGIA AND LOSS OF SOMESTHETIC GENITAL STIMULI

It is understood that paraplegia per se (motor paralysis of the legs and the lower part of the body) does not lead to loss of sexual excitation. This is borne out by observations on a number of poliomyelitic patients used as controls.

Since the endocrine and psychic systems are likewise not responsible for the sexual deficit, the only causative factor remaining is the loss of somesthetic stimuli from the genital organs.

Foerster[18] lent credence to the important role of such stimuli when he stated:

> The pleasant or unpleasant character of sensation is definitely related to conduction in the ventrolateral columns. In bilateral destruction of these columns there is apparently complete loss of these affect qualities such as itching, tickling and libidinous feeling.

Hirschfeld also supported the role propounded by his case history of a soldier who was wounded in World War I by a bullet which passed through the lumbar region of his body and pierced the spinal cord. This author stated:

> In sexual regard, the libido . . . had completely vanished. Every feeling of pleasure was also lacking.[11]

17. Fenichel, O.: The Psychoanalytic Theory of Neurosis, New York, W. W. Norton & Company, Inc., 1945.

18. Foerster, O., cited by Strong and Elwyn: Human Neuroanatomy, Baltimore, Williams & Wilkins Company, 1943, p. 120.

Further evidence for the conclusion that somesthetic stimuli are necessary for the elaboration of sexual excitation is strikingly demonstrated by 2 cases.

The first case is that of a married, unemployed white man aged 28 who in May 1948 was hurled from the back seat of a car through the canvas roof. The patient thought that he landed on his buttocks and remembered sitting with his back propped against the running board a minute or so after the accident. He was paralyzed in both lower extremities and within five hours experienced numbness and pins and needles sensations over the lower half of his body. He was hospitalized and told that he had a compression of the twelfth thoracic vertebra.

Improvement was gradual. For the first four weeks the patient had no sexual thoughts or feelings. At the end of this time he had his first spontaneous erection and a surge of sexual libido. In the interim there had been an increasing return of somesthetic stimuli. The patient formerly owned his own business, but after the accident he lost interest and decided it was too much responsibility.

The second case is that of a salesman aged 52, who in June 1944, at the age of 47, had onset of numbness over the lower half of the body from the umbilicus downward, difficulty in walking and complete disappearance of sexual libido. He was hospitalized at the Neurological Institute of New York in December 1944. Study revealed that he had Paget's disease (osteitis deformans) affecting the vertebrae. The eighth, ninth and tenth thoracic vertebrae impinged on the cord. A decompression operation was performed in June 1945. The spines of the involved vertebrae were removed. After operation, motor power in his legs became stronger and there was some improvement in the sensory modalities, but sensation from the external genitalia was still greatly impaired. His sexual libido remained absent.

The patient was permitted to convalesce at home. Improvement continued for several weeks, but his original symptoms then recurred. He was hospitalized again, and a myelogram showed block at the fifth thoracic vertebra. A second decompression was done in June 1946, with removal of the spines of the fifth, sixth and seventh thoracic vertebrae. There was marked progressive improvement in walking and in sensory perception. The libido returned to a "normal" stage. He had active sexual phantasies, and he experienced sexual excitement and desire for intercourse, which he eventually satisfied. Function during the act was good. It is interesting that after the first operation, when sexual activity was absent, the patient had little or no interest in work and sat at home unemployed. After the return of his sexual functions, his interest in his environment heightened, and he returned to work. The same sagging of interest during loss of libido has been noted in the

other patients of this series and seems to confirm the impression that normal daily activities are invested with a certain amount of sexual libido.

One is led to the conclusion that in cases of complete transections of the cord the absence of genital stimuli, which are otherwise destined for the medullary and higher centers of the brain, is responsible for the patient's failure to develop sexual excitation. Mental activity, wishes, memories and phantasies, together with hormone activity, are not enough to "trip the switch" when the specific libidinous sensory stimuli from the genitalia are absent.

SUMMARY AND CONCLUSIONS

The role of somesthetic stimuli in the development of sexual excitation in man was investigated.

Nineteen paraplegic patients were studied. Twelve had "complete" transections of the cord, and 7 had partial transections. Four of the cases of complete transection are described in detail.

None of the 4 patients experienced sexual excitation at any time after his injury.

The endocrine and psychic systems were ruled out as causative factors.

Evidence is adduced to show that the loss of somesthetic stimuli from the genital organs is primarily responsible for the absence of sexual excitation.

SECTION OF U FIBERS OF MOTOR CORTEX IN CASES OF PARALYSIS AGITANS (PARKINSON'S DISEASE)

Report of Nine Cases

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AT THE meeting of the Harvey Cushing Society in San Francisco in April 1948, Russell Meyer reported the successful relief of the symptoms in a patient with hemiballismus by an incision in area 4 of Brodmann on the side opposite the movement. The incision was 2.5 cm. deep and 6 cm. long, without any removal of cortical tissue. It was designed to interrupt the U fibers connecting area 4 with area 6.

Dr. Barry Wyke, of Sydney, Australia, who heard this presentation and saw the motion picture, was so impressed with the results that later, at the meeting of the American Neurological Association in June 1948, he suggested to several neurologists and neurosurgeons that a somewhat similar operation might relieve the rigidity and tremor of paralysis agitans (Parkinson's disease).[1] The plan was to locate area 4 s by stimulation at operation. Such stimulation was said to cause cessation of tremor and rigidity in the contralateral limbs. An incision anterior to this area was then to be carried out, to interrupt the fibers running from area 6 to area 4 s. The theory apparently was that if such fibers existed they would probably act on area 4 s in an inhibitory way. Since stimulation of area 4 s was said to cause inhibition of tremor and rigidity in the contralateral limbs, it was to be expected that release of this area

1. Dr. Meyer had participated with Mr. W. Lister Reid, F.R.C.S., in Sydney, Australia, in some of the cases of cortical resections on patients with Parkinsonism and in 1 case in which the U fibers were sectioned without removal of cortical tissue but with undercutting of the cortex. The results were all indifferent. He had also participated in experimental surgery on dogs with a tremor-rigidity syndrome. (Reid, W. L.: Studies on the Tremor-Rigidity Syndrome: I. Surgical Treatment of Human Subjects, M. J. Australia **2**:481, 1948. McGovern, V. J.; Wyke, B. D.; Dodson, M. E., and Steel, J.: Effect of Surgery upon Canine Tremor-Rigidity Syndrome, ibid. **2**:492, 1948).

from the control of area 6 would have a similar effect. These suggestions were taken seriously by a group of neurosurgeons, who have performed this operation in a total of 9 cases.

REPORT OF CASES

We present a brief report of the 9 cases. Our purpose in publishing this material is to report the failure of the procedure, for too many patients with paralysis agitans had already had their hopes raised.

Of the 9 patients, the youngest was 37 and the oldest 59 years of age. The duration of the disease varied from one and one-half years, for the oldest patient, to nine or ten years, for a patient aged 44. Seven of the patients did not have associated vascular disturbance, such as arteriosclerosis or hypertensive vascular disease. Four were men and 5 were women. In 5 the disease was unilateral, and

*Summary of Data in Nine Cases of Section of U Fibers for Relief of Parkinsonism**

Case	Age, Yr.	Duration of Disease, Yr.	Surgeon	Sex	Diagnosis	State of Disease	Unilateral or Bilateral	Result
1	43	8	Scarff	M	Postencephalitic parkinsonism	Severe	Unilateral	Unimproved
2	53	2	Scarff	M	Postencephalitic parkinsonism	Moderate	Unilateral	Unimproved
3	37	5	Scarff	M	Postencephalitic parkinsonism	Moderate	Unilateral	Unimproved
4	49	9	White	F	Postencephalitic parkinsonism	Severe	Bilateral	Unimproved
5	41	5	White	F	Postencephalitic parkinsonism	Moderate	Bilateral	Slightly improved (subjectively)
6	44	10	Pool	F	Postencephalitic parkinsonism	Moderate	Unilateral	Slightly improved
7	45	8	Pool	F	Paralysis agitans	Severe	Bilateral	Unimproved
8	59	8	Pool	F	Parkinson's disease and arteriosclerosis	Severe	Bilateral	Worse
9	59	1½	Walker	M	Parkinson's disease and arteriosclerosis	Moderate	Unilateral	Worse (died at home 6 mo. after operation)

* This table represents reports one year after operation.

in 4, bilateral. None of the 9 patients would be regarded as having a mild form of paralysis agitans, 5 having a moderately severe form and 4 as having very severe disease. In only 1 (case 7) was localization of the suppressor area proved by stimulation with reduction in the rigidity and movements. In the other 8 patients no clearcut reduction of symptoms was seen after area 4 s was stimulated in the operating room. The technic of the operation was not difficult, and there were no operative complications worthy of note. The postoperative state of all 9 patients was reasonably satisfactory from the standpoint of the surgeon, although all of them showed evidences of paralysis of the opposite extremities for a variable length of time, together with aphasia when the operation was done on the dominant hemisphere.

A follow-up study of these 9 patients was made approximately one year after the operation, and the results are summarized in the accompanying table, which shows clearly that, except for questionable and mild improvement in 2 patients, respectively, this operation gives no promise of relief of symptoms in paralysis agitans. Six of the patients were definitely worse, having residual hemiplegia or aphasia that persisted during the one year period of observation. In only 1 of the 9 cases was any objective evidence of improvement apparent on neurologic

examination, performance tests or the electromyogram. One of the patients still maintains that she feels better, but the improvement is entirely subjective. Another patient had a subsequent prefrontal lobotomy for a depression, and this patient is somewhat better on the whole than she was prior to her operations, but the effect of the lobotomy must be considered as at least partially responsible for her improved state of mind. In this patient, there is some objective evidence of improvement in that she walks better.

Since this report is a negative one, and made with the purpose of discouraging other surgeons from doing this procedure, we have purposely left out a discussion of the operative technic and the details of the clinical and laboratory examinations, both preoperative and postoperative. In all these cases, however, complete operative notes and preoperation and postoperation clinical studies, including psychologic tests in some cases, motion pictures and electromyographic observations, were made. In 6 of the 9 cases photographs were made of the exact site of the operation. These data are available to any one who is interested in consulting the neurosurgical authors.

CEPHALIN-CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS IN SCHIZOPHRENIA

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IN RECENT years interest has been displayed in the problem of hepatic function in schizophrenia. In a study concerned with the detoxication of benzoic acid in schizophrenia, Quastel and Wales [1] first reported decreased synthesis and excretion of hippuric acid by catatonic patients. The observation that all of a group of 18 catatonic patients excreted subnormal quantities of hippuric acid led these authors to the conclusion that a metabolic disturbance of the liver affecting detoxication of benzoic acid may be a characteristic feature of catatonia. Ström-Olsen and associates [2] were unable to confirm this observation, as only 5 of their 28 patients exhibited decreased synthesis and output of hippuric acid. The results of Finkelman and associates [3] were somewhat equivocal. These investigators indicated that the average excretion of hippuric acid in 17 catatonic subjects was below normal. However, it is pertinent to note that 9 of their patients had values above the normal level, while 8 had levels below normal. The results for all of 9 hebephrenic patients were normal. The authors postulated that the decreased excretion of hippuric acid might be due to the phenomena of muscular rigidity and immobility in catatonic patients, and they drew attention to the values for a hebephrenic patient whose excretion of hippuric acid fell considerably while he was immobilized in a body cast but returned to normal levels when he regained his usual motor activity. The report of Michael, Looney and Borkovic [4] cast further doubt on the validity of previous studies. It was

From the Fairfield State Hospital.

1. Quastel, J. H., and Wales, W. T.: Faulty Detoxication in Schizophrenia, Lancet **2**:301 (Aug. 6) 1938.

2. Ström-Olsen, R.; Greville, G. D., and Lennon, R. W.: Hippuric Acid Synthesis in Schizophrenia, Lancet **2**:995 (Oct. 29) 1938.

3. Finkelman, I.; Hora, J.; Sherman, I. C., and Horwitt, M. K.: Detoxication of Sodium Benzoate in Neuropsychiatric Disorders, Am. J. Psychiat. **96**:951 (Jan.) 1940.

4. Michael, S. T.; Looney, J. M., and Borkovic, E. J.: Synthesis of Hippuric Acid in Dementia Precox, Arch. Neurol. & Psychiat. **52**:57 (July) 1944.

pointed out that the rate of synthesis of hippuric acid is correlated with body size,[5] a factor which had been neglected in previous work. Michael and associates found no difference in the average amount of sodium benzoate detoxicated per unit of body weight in 18 catatonic patients and in 9 control subjects. However, there was a somewhat greater range of results among the patients, as 3 had levels lower than the lowest value for the controls and an equal number had levels exceeding the highest normal readings. A similar variability, usually within normal extremes, has been observed in schizophrenic patients with respect to other physiologic and biochemical processes. Wong [6] found normal excretion of bromsulphalein in schizophrenic persons. However, excretion of hippuric acid was definitely low in patients with simple and with catatonic schizophrenia and was somewhat subnormal in the hebephrenic and paranoid subgroups. It must be emphasized, however, that the factor of body size was not taken into consideration. Wong also gained the impression that the excretion of hippuric acid appeared to vary somewhat according to the degree of motor activity. He, as well as other observers,[7] questioned the effect of such factors as nutritional status and absorption from the gastrointestinal tract on the results obtained.

The cephalin-cholesterol flocculation test of Hanger [8] has also been used as a measure of hepatic function in cases of schizophrenia. A report by De Jong and St. John [9] indicated that 46.8 per cent of 32 catatonic patients, 44.6 per cent of 56 female patients with noncatatonic schizophrenia and 15.2 per cent of 59 male patients with noncatatonic schizophrenia gave positive reactions to cephalin flocculation tests, as compared with 6.9 per cent of 121 control subjects. These results, and other data, led De Jong [10] to formulate the theory that hepatic damage may be a primary factor in the appearance of catatonic features in both human and animal subjects and in the development of certain symptoms of noncatatonic schizophrenia. He expressed the opinion that a pathologic metabolite may exert a toxic influence on the central nervous system, thereby accounting for manifest clinical symptoms. In a more recent report,

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5. Scurry, M. M., and Field, H.: Correlation of the Intravenous Hippuric Acid Test of Liver Function with Body Size, Am. J. M. Sc. **206**:243 (Aug.) 1943.

6. Wong, Y. T.: The Hippuric Acid Liver Function Test in Schizophrenia, J. Nerv. & Ment. Dis. **92**:173 (Aug.) 1945.

7. Discussion on paper by Finkelman, Hora, Sherman and Horwitt.[3]

8. Hanger, S. M.: The Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, Tr. A. Am. Physicians **53**:148, 1938.

9. De Jong, H., and St. John, J. H.: The Cephalin-Cholesterol Flocculation Test in Catatonic and Other Schizophrenics, J. Nerv. & Ment. Dis. **101**:572 (June) 1945.

10. De Jong, H. H.: Experimental Catatonia, Baltimore, Williams & Wilkins Company, 1945.

Zimmerman, Gallavan and Eaton [11] failed to confirm De Jong's results. These investigators found no increase in the percentage of positive reactions to cephalin flocculation tests in a series of 175 schizophrenic patients as compared with that for 210 nonschizophrenic psychiatric patients. However, there was no separate subgroup of catatonic patients in this first phase of their study. A small group of chronically ill catatonic and noncatatonic patients with long hospitalizations also failed to exhibit positive results in the cephalin flocculation tests.

In view of the lack of uniformity in the results of these two studies, it was felt that further data might be helpful in this matter. Accordingly, a

TABLE 1.—*Diagnostic Classification of 878 Psychiatric Patients*

	Schizophrenia						Nonschizophrenic Mental Illness							
	Simple	Hebephrenic	Catatonic	Paranoid	Mixed	All Types	Involutional	Manic-Depressive Psychosis	Alcoholic States	Senile Arteriosclerotic Psychosis	Psychoneurosis	No Psychosis	Other Psychiatric Illness	All	Totals
Female	15	13	45	47	13	133	31	62	18	93	27	12	29	272	405
Male	13	18	25	41	11	108	11	32	103	97	31	38	53	365	473
Total	28	31	70	88	24	241	42	94	121	190	58	50	82	637	878

TABLE 2.—*Incidence of Positive Reactions to Cephalin Flocculation Tests in 878 Psychiatric Patients*

	Female			Male			Total		
		Positive Readings			Positive Readings			Positive Readings	
	Total No.	No.	Per Cent	Total No.	No.	Per Cent	Total No.	No.	Per Cent
Catatonic schizophrenia	45	2	4.4	25	0	0	70	2	2.9
Noncatatonic schizophrenia	88	4	4.6	83	0	0	171	4	2.3
Nonschizophrenic mental illness	272	8	2.9	365	15	4.1	637	23	3.6
Total	405	14	3.5	473	15	3.1	878	29	3.3*

cephalin-cholesterol flocculation test was performed on all patients admitted to the Fairfield State Hospital during a period of approximately one year. The diagnostic classification of the series is indicated in table 1.

Readings greater than 2 plus were regarded as positive. Results of the cephalin flocculation test are summarized in table 2.

It is evident that the incidence of positive results in the cephalin flocculation test was no higher among catatonic or schizophrenic patients

11. Zimmerman, F. H.; Gallavan, M., and Eaton, M. T.: The Cephalin-Cholesterol Flocculation Test in Schizophrenia, Am. J. Psychiat. **105**:225 (Sept.) 1948.

than among patients in other diagnostic categories. In fact, among male patients there was greater positivity in the nonschizophrenic group owing possibly to the relatively high incidence of alcoholic intoxication and other organic conditions with clinically unrecognizable hepatic disease.

Since this series was composed largely of patients in a moderately early stage of mental illness, we next studied two groups of chronically ill patients with long term hospitalizations, namely, 202 schizophrenic persons, for most of whom the original diagnosis was catatonic schizophrenia, and 100 controls, consisting of patients with other types of mental illness. The durations of hospitalization were similar in the two groups. Thus for 71 per cent of the schizophrenic patients the period of hospitalization was not longer than ten years, and for 29 per cent, over a decade; the corresponding figures for the control group were 72 and 28 per cent, respectively. The data are summarized in table 3.

TABLE 3.—*Results of Cephalin Flocculation Test in Patients Chronically Ill with Schizophrenia*

	Females			Males		
	Total No.	Positive Readings		Total No.	Positive Readings	
		No.	Per Cent		No.	Per Cent
Schizophrenia						
Simple	1	0	0	2	0	0
Hebephrenic	3	0	0	4	0	0
Catatonic	95	11	11.6	60	25	41.7
Paranoid	4	1	25.0	2	1	50.0
Mixed	16	2	12.5	15	3	20.0
Total no. with schizophrenia	119	14	11.8	83	29	34.9
Controls	50	6	12.0	50	0	0

It is apparent that among female patients the incidence of positive results was practically identical for the groups with catatonic and noncatatonic schizophrenia and the controls, although the results were significantly higher than for the first series of newly admitted female patients. Among the male patients, however, one notes a striking difference between the groups with catatonic or noncatatonic schizophrenia and the controls.

It is pertinent that the laboratory tests on this series of chronically ill, long-hospitalized patients was performed during the summer months. In view of a previous report [12] on photosensitivity in the production of falsely positive results in the cephalin flocculation test, 36 of the 49 tests giving positive results were repeated approximately six months later, i. e., during the winter season. All the readings were negative at the second examination.

12. Neefe, J. R., and Reinhold, J. G.: Photosensitivity as a Cause of False Positive Cephalin-Cholesterol Flocculation Tests, Science **100**:83 (July 28) 1944.

Thymol turbidity tests, according to a slight modification of the Maclagan [13] method, were also performed on 297 of the chronically ill, long-hospitalized patients. The results are summarized in table 4. It is evident that the readings were essentially negative and that there was no significant difference between the results for the groups with catatonic or noncatatonic schizophrenia and those for the controls.

CONCLUSIONS

This study does not appear to offer any evidence in support of the theory advanced by De Jong that disturbed hepatic function, as measured by abnormalities in the results of the cephalin-cholesterol flocculation test, is an etiologic factor in the production of catatonic symptoms or schizophrenia. Thus, the incidence of positive results in cephalin flocculation

TABLE 4.—*Results of Thymol Turbidity Test in Patients Chronically Ill with Schizophrenia*

	Females				Males			
		Readings, Units				Readings, Units		
	Total No.	Normal (0-5)	Borderline (5-7)	Elevated (7+)	Total No.	Normal (0-5)	Borderline (5-7)	Elevated (7+)
Schizophrenia								
Simple	1	1	0	0	2	2	0	0
Hebephrenic	3	3	0	0	4	4	0	0
Catatonic	95	89	4	2	60	59	0	1
Paranoid	4	4	0	0	2	2	0	0
Mixed	16	15	1	0	15	15	0	0
Total no. with schizophrenia	119	112	5	2	83	82	0	1
Controls	45	43	1	1	50	46	4	0

tests was no greater in a group of newly admitted patients with catatonic or noncatatonic schizophrenia with illnesses of relatively recent origin than in psychiatric patients with other types of mental illnesses. Results for a group of chronically ill patients with long hospitalizations are not fully crystallized. At the original examination, among females, the incidences of positive results in cephalin flocculation tests were identical for patients with catatonic and noncatatonic schizophrenia and for the controls, but the degree of positivity was higher than that for newly admitted patients; among males, the incidence of positive results was definitely greater for catatonic or noncatatonic schizophrenic patients than for the chronically ill, long-hospitalized controls and/or the newly admitted patients. However, repetition of the test at a later date, during the winter season, in most of the cases with positive results gave uniformly negative results. Several possible explanations for this phenomenon

13. Maclagan, N. F.: Thymol Turbidity Test: New Indicator of Liver Dysfunction, Brit. J. Exper. Path. 25:234 (Dec.) 1944.

present themselves. First, as indicated by Neefe and Reinhold,[13] the test is affected by photosensitivity and must be performed under rigidly controlled conditions; second, it is possible that dietary and nutritional factors exert an influence, and, third, there is the possibility of greater flux in the physiologic stability of the schizophrenic organism.

It is unlikely that a frank pathologic process in the liver would have reversed itself completely in all cases within a span of six months. The negative results in thymol turbidity tests performed at the time of the original examinations also lends evidence in support of the belief that hepatic damage was absent.

SUMMARY

The incidences of positive results in cephalin-cholesterol flocculation tests were almost identical among newly hospitalized catatonic patients, patients with noncatatonic schizophrenia and other psychiatric patients. Results for a chronically ill group with long term hospitalization were somewhat equivocal. The results of thymol turbidity tests for chronically ill patients were essentially negative. This study does not lend confirmation to a previously expressed theory that hepatic damage is an etiologic factor in the production of catatonia or other schizophrenic symptoms.

Miss Florence Pease and co-workers gave technical assistance in this study.

TRANSSYNAPTIC DEGENERATION IN THE VISUAL SYSTEM

Report of a Case

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THE OCCASION for this report was the finding of progressive development of bilateral primary optic nerve atrophy five and one-half years after an extensive penetrating gunshot wound of both occipital lobes. There was no definite evidence of injury to the optic nerves or tracts to account for this atrophy, and it appeared probable that a transsynaptic degeneration had occurred. A search of the literature revealed that transsynaptic degeneration in the visual system had been mentioned by several writers but that few case reports had been included. Because degeneration of the optic nerve is not ordinarily anticipated after lesions of the occipital lobe, we believe it advisable that this problem be reviewed.

When an axon within the central nervous system is sectioned, the distal segment degenerates up to the synapse but produces no pathologic change in the cell on which it terminates. There are a few instances in which degeneration of an axon not only progresses up to the synapse but also effects degenerative changes in the contiguous neuron. This phenomenon is called transneuronal,[1] or transsynaptic degeneration.[2] It occurs in an area that, deriving its innervation predominantly from one source, becomes isolated from its chief source of innervation. The best known example is the degeneration of the lateral genticulate bodies following destruction of the neurons in the retina.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Fulton, J. F.: Physiology of the Nervous System, ed. 2, London, Oxford University Press, 1943, p. 38. (*b*) Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 390.

2. Polyak, S.: The Nervous System, in Maximow, A., and Bloom, W.: Textbook of Histology, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 173.

The changes in the geniculate bodies following lesions of the optic nerve have been demonstrated in experimental and clinical material. Minkowski [3] found in experimental animals that several weeks after one eye had been removed the cells of the lateral geniculate bodies showed chromatolytic changes. Brouwer and Zeeman [4] have since used this method to study the connections of the retina with the cells in the geniculate bodies. Henschen [5] reported 3 cases in which certain of the cellular laminas of the human lateral geniculate body showed degenerative changes after enucleation of one eye. Clark [6] described the autopsy observations on a woman whose left eye had been removed because of glaucoma two years before death. There was complete chromatolysis in the corresponding laminas of the lateral geniculate bodies.

The degeneration following lesions of the optic nerve need not be limited to the external geniculate body but may even progress into the striate area. Juba and Szatmari [7] observed degenerative changes in the striate area of the cortex in 1 of their cases.

This direction of degeneration from the optic nerves and tracts to the lateral geniculate bodies and then to the calcarine area is the usual one, and is what is usually implied when reference is made to transsynaptic degeneration in the visual system. However, the effect of injury to the occipital lobes is not so clear. Polyak's [8] opinion that transsynaptic degeneration following injury to the occipital lobe is unlikely is widely held. Reports on collections of cases [9] of lesions of the occipital lobe have failed to mention any secondary effects on the optic nerves. In a case of a 20 year old man who had been blind since

3. Minkowski, M.: Experimentelle Untersuchungen über die Beziehungen der Grosshirnrinde und der Netzhaut zu den primären optischen Zentren, besonders zum Corpus geniculatum externum, Arb. a. d. hirnanat. Inst., Zürich **7**:255, 1913.

4. Brouwer, B., and Zeeman, W. P. C.: The Projection of the Retina in the Primary Optic Neuron in Monkeys, Brain **49**:1 (March) 1926.

5. Henschen, S. E.: Die Vertretung der beiden Augen in der Sehbahn und in der Sehrinde, Arch. f. Ophth. **117**:419, 1926.

6. Clark, W. E. L.: A Morphological Study of the Lateral Geniculate Body, Brit. J. Ophth. **16**:264 (April) 1932.

7. Juba, A., and Szatmari, A.: Ueber seltene hirnanatomische Befunde in Fällen von einseitiger peripherer Blindheit, Klin. Monatsbl. f. Augenh. **99**:173 (Aug.) 1937.

8. Polyak, S.: Personal communication to the authors.

9. (*a*) Scarlett, H. U., and Ingham, S. D.: Visual Defects Caused by Occipital Lobe Lesions: Report of 13 Cases, Arch. Neurol. & Psychiat. **8**:225 (Sept.) 1922. (*b*) Greear, J. N., Jr., and McGavic, J. S.: Visual Disturbances Associated with Head Injuries, Arch. Ophth. **36**:33 (July) 1946. (*c*) Austin, G. M., Jr.; Lewey, F. H., and Grant, F. C.: Studies on the Occipital Lobe: I. Significance of Small Areas of Preserved Central Vision, Arch. Neurol. & Psychiat. **62**:204 (Aug.) 1949.

birth,[10] the optic nerves and tracts were normal, despite bilateral microgyria of the calcarine area and severe gliosis of the lateral geniculate bodies.

On the other hand, there are both opinion and data favoring the view that the optic nerves are affected by lesions of the occipital region. Oppenheim [11] referred to the "still unexplained" atrophy of the optic nerves that occurs many years after an injury to the occipital lobe. Wilbrand and Saenger [12] also stated that this type of transsynaptic degeneration was possible in unusual cases, particularly if the occipital involvement occurred during fetal life or early childhood. More recently Walsh[1b] has stated that in some cases of cortical blindness there develops outspoken optic nerve atrophy, usually after the passage of several years. He further stated that it is not known why this occurs in some instances and not in others. Klüver [13] reported decrease of the staining properties of the left halves of the retinas four years after extirpation of the left occipital cortex of a rhesus monkey. There are also clinical reports of injury to the occipital lobe followed by optic nerve atrophy which was attributed to transsynaptic degeneration. In 1 of these reports [14] a man aged 53 was found to have left homonymous hemianopsia and bilateral primary optic nerve atrophy when examined eighteen years after he had received a gunshot wound in the right occipital region. The only other neurologic abnormality was the presence of grand mal seizures. The other report [15] described a woman aged 51 whose only neurologic deficit consisted of right homonymous hemianopsia, pronounced optic nerve atrophy on the right and mild optic nerve atrophy on the left. There was an osseous depression in the left parieto-occipital region as a result of a head injury sustained more than thirty years previously. Both reports concluded that the optic nerve atrophy represented a transsynaptic degeneration.

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10. Tokay, L.: Blindheit bei doppelseitiger Mikrogyrie der Calcarinagegend, Arch. f. Ophth. **129**:426, 1933.

11. Oppenheim, H.: Text-Book of Nervous Diseases for Physicians and Students, translated by A. Bruce, ed. 5, Edinburgh, Otto Schulze & Company, 1911, vol. 1, p. 124.

12. Wilbrand, H., and Saenger, A.: Die Erkrankungen des Opticusstammes, in Die Neurologie des Auges, Wiesbaden, J. F. Bergman, 1913, vol. 5.

13. Klüver, H.: Certain Effects of Lesions of the Occipital Lobes in Macaques, J. Psychol. **4**:383 (Oct.) 1937.

14. Euzière, J.; Viallefont, H., and Vidal, J.: Double atrophie optique et hémianopsie gauche consécutives à une blessure occipitale droite, Arch. Soc. d. sc. méd. et biol. de Montpellier **4**:212 (April) 1933.

15. Fledelius, M.: A propos de l'hémianopsie d'origine traumatique, Arch. d'opht. **51**:561 (Sept.) 1934.

It is thus evident that transsynaptic degeneration following injury to the posterior neuron of the visual system is an unsettled problem. Neither the experimental nor the clinical observations have provided a clearcut answer.

REPORT OF CASE

E. A. R., a white man aged 26, a veteran of World War II, was admitted to the Winter Veterans Administration Hospital for the first time on Nov. 1, 1948 because of a grand mal seizure which had occurred six weeks previously. In 1942 his vision was recorded as 20/20. On May 12, 1943 he sustained a penetrating head wound, with the shell fragments entering the left occipital region. He was unconscious for about a week, and on regaining consciousness complained of complete loss of vision. Three weeks after the injury he could only distinguish light from dark and recognize the examiner's hand at 2 feet (60 cm.). Macular vision was preserved but diminished. Both pupils were dilated, reacted sluggishly to light and failed to constrict on convergence. Field hospital records indicated impairment of upward gaze, vertical nystagmus, engorgement of the retinal veins and papilledema of 3 D. There was no mention of retinal exudate, blurring of the disk margins, bulging of the wound in the region of the defect in the skull or other evidence of increased intracranial pressure at this time. Except for a Babinski response on the right, the rest of the neurologic examination revealed no abnormality.

On June 2, 1943 four fragments of bone were removed from the brain in the occipital region. The wound was described as being located above the tentorium and to the left of the superior longitudinal sinus, and at its entrance measuring 5 by 10 cm. Roentgenograms of the skull on June 4 revealed a wedge-shaped fracture under the left lambdoid suture which measured 1 by 6 cm. and a linear fracture extending into the parietal and occipital bones on the left. There was no roentgenologic evidence of chronic increased intracranial pressure. Furthermore, spinal fluid pressures at this time made the previous assertion of 3 D. of disk choking extremely questionable.

Lumbar punctures on June 5, June 10 and June 21 revealed pressure readings of 225, 240 and 240 mm. of water, respectively. The fluid was clear on each occasion, and laboratory examination on June 5 revealed 80.6 mg. of protein per hundred cubic centimeters, a trace of globulin, a colloidal gold curve of 2100000000 and 9 white blood cells per cubic millimeter.

On June 10 the patient could tell black from white and round from square and was able to identify a yellow pencil. Examination on July 9 revealed that no papilledema was present. On July 10 he could count fingers at 2 feet (60 cm.) with each eye. The pupils were partially dilated and reacted to light, though somewhat sluggishly. Neither optic disk showed any definite change at this time.

On August 17 surgical exploration in the region of the wound revealed a large cystic cavity which occupied the entire left occipital lobe and at the bottom of which the lateral ventricle could be seen communicating with the lesion. The picture was that of almost complete absence of the left occipital lobe. It was the surgeon's opinion that similar damage, but to a less extent, had occurred in the right occipital lobe, thus explaining the patient's bilateral amblyopia.

Examination on September 20 revealed uncorrected vision of 4/200 on the right and 3/200 on the left, correctible to 5/200 on each side. Examination of the visual fields showed right homonymous hemianopsia, with a greater amount of vision retained on the right. The pupils and fundi were now reported to be normal.

An electroencephalogram on October 1 showed nearly total absence of alpha frequency. This was more complete on the left side, especially posteriorly. His looking into light caused the alpha potential to disappear.

Examination on April 21, 1944 revealed ability to count fingers at 5 feet (150 cm.) with the right eye and at 3 feet (90 cm.) with the left eye. Large physiologic cups were described in both optic disks, but no funduscopic abnormalities to account for his poor vision were present. Hemianoptic pupillary responses were obtained bilaterally.

The next examination, on Dec. 2, 1946, revealed uncorrected vision of 5/400, correctible to 5/400, in the right eye and of 3/400, correctible to 3/400 in the left eye. Peripheral fields showed contraction bilaterally, with right homonymous hemianopsia. There was temporal pallor of both optic disks, but otherwise the fundi were normal. A diagnosis of early bilateral optic nerve atrophy was made at this time, three and one-half years after the injury.

On Sept. 21, 1948 the patient had a typical grand mal seizure, and on November 1 he entered Winter Veterans Administration Hospital for treatment of this com-

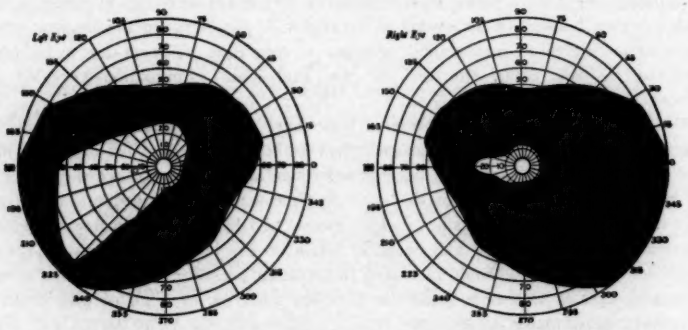

Fig. 1.—Visual fields five and one-half years after injury to the occipital lobes.

plication. He stated that there had been gradual improvement in his vision for the first three months after injury but that there had been no change since. General physical examination at this time revealed a triangular defect in the skull, about 3 cm. in diameter, in the left occipital region. Neurologic examination revealed that the pupils were slightly dilated, round and equal and that they responded to light and in accommodation. Funduscopic examination showed chalky pallor of both disks. The nasal half of the left disk retained its normal appearance to a slight degree, although the nasal half of the right disk was atrophic. The margins of the disks were sharp and distinct, and no exudates were present. The lamina cribrosa was readily evident, and there was attenuation of the vessels. Bilateral primary optic nerve atrophy was now apparent and was much more advanced than that described two years before. There was a marked visual loss bilaterally, limiting him to recognition of gross objects. Vision was 10/400 on the right and 5/400 on the left. The visual fields (fig. 1) showed right homonymous hemianopsia with constriction of the peripheral fields, especially on the right. These fields were essentially the same as those recorded five years previously except that there had been progressive constriction of fields on the right. There was no spatial disorientation or visuognostic disturbance.

The spinal fluid pressure was 120 mm. of water, and laboratory examination of the spinal fluid showed a normal state. Pneumoencephalographic studies, (fig. 2) performed on November 18, showed the entire left lateral ventricle to be greatly enlarged, especially in the occipital horn. The latter had the configuration of a sphere and was approximately four times the normal size. The right lateral ventricle was also enlarged, especially in the occipital horn, but less so than the left. Very little subarachnoid gas could be seen over either hemisphere. The third and fourth ventricles, the aqueduct, the cisterna pontis and the cisterna magna were all normally outlined. There was a large accumulation of air in the region of the optic chiasm. The electroencephalogram showed moderate asymmetry of alpha production, with both faster and lower voltage waves appearing in the left occipital region in greater number than in the right. There was also flattening of

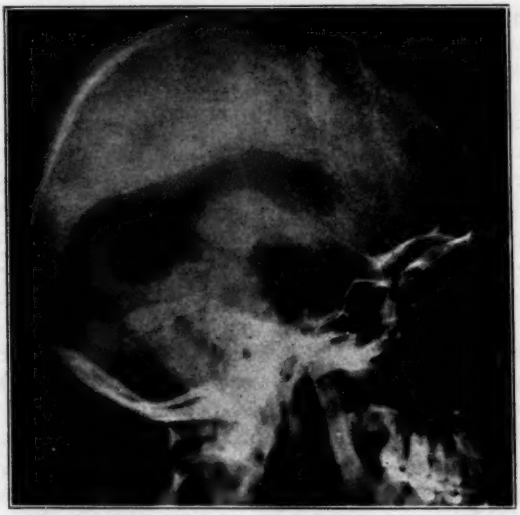

Fig. 2.—Traumatic porencephaly of the left occipital lobe. There was a similar, but much less severe, involvement on the right.

the waves on the left. Brief runs of 6 to 7 cycles per second waves of 30 to 40 microvolts were seen in all leads, but were more pronounced on the left side. Attempts at photic driving failed to influence the cerebral rhythm.

Reexamination on April 1, 1949 showed no change in the patient's clinical status.

COMMENT

The important feature of this case was a penetrating head wound through both occipital lobes but more extensive on the left than on the right. For the first three months after the injury there was gradual improvement of vision, but from then until our examination, five years later, the patient's vision remained essentially unchanged. During the same period there slowly developed a severe primary optic nerve

atrophy bilaterally. This atrophy was observed for the first time three and one-half years after the injury and had progressed to a marked degree at the time of our examination, five and one-half years after the injury.

It is thought that the optic nerve atrophy represented a transneuronal degeneration. However, other explanations were considered. That there may have been an injury to some part of the visual system anterior to the lateral geniculate bodies to account for the primary optic nerve atrophy was taken into account. An examination three weeks after the injury revealed weakness of upward conjugate gaze, mild vertical nystagmus, sluggish pupillary reactions to light and failure of the pupils to constrict on convergence. But these findings were transitory, and there has been nothing subsequent to indicate permanent focal damage in the region of the midbrain or the optic chiasm. The possibility of a fracture in the region of the optic foramens as a cause of injury to the optic nerves was discounted because roentgenograms of this area showed no such conditions. Concussion to the optic nerves or tracts or hemorrhage into the surrounding tissues along these pathways, with resultant compression of the nerve fibers, may be invoked as explanations but cannot be confirmed by the clinical evidence at hand.

The possibility that this condition is an atrophy of the optic nerve secondary to the alleged 3 D. of choking of the disk can be discounted because there was no bulging of the wound at the defect in the skull, and any increased intracranial pressure sufficient to produce choked disk had subsided within three weeks, a period too brief to produce optic nerve atrophy. Furthermore, the distinct disk margins, the prominent lamina cribrosa and excavated disks and the absence of any old exudates or of gliosis indicated clearly that the atrophy of the optic nerve was primary, and not secondary.

In both the other case reports [16] in which optic nerve atrophy followed injury to the occipital area, as well as in the monkey in which this occurred,[13] a considerable period had elapsed from the time of injury until the changes in the optic nerves were observed. That several years must elapse before outspoken atrophy occurs appears likely. In our case the first indications of atrophy were noted three and one-half years after the lesion. Other salient points in our case which appear to favor transsynaptic degeneration as the explanation of the optic nerve atrophy are (1) the occurrence of slowly progressive primary optic nerve atrophy over a period of five years, while vision remained essentially unchanged; (2) the finding at the time of our examination of a more pronounced atrophy in the nasal half of the

16. Euzière, Viallefont and Vidal.[14] Fledelius.[15]

right optic disk than in the nasal half of the left optic disk, a finding which is consistent with the presence of more extensive destruction of the left occipital lobe than of the right, and (3) the absence of any residual extraocular palsy or pupillary disturbance, which might be expected if there had been an injury in the region of the optic chiasm.

The observations in our case, together with those reported in the 2 similar cases, are certainly not enough to justify the conclusion that transsynaptic degeneration is a constant finding in the optic nerves after injuries to the occipital lobes. More reports on cases followed carefully over a long period are needed before one can draw such a conclusion. That some factor such as bilateral rather than unilateral involvement of the occipital area might be of importance can be determined only by the report of more cases. Recognition that injury along the optic nerves and tracts with resultant optic nerve atrophy occurs many times with only slight head injury, or with the injury at some distant point, tends to make one even more cautious.[17] Nevertheless, such a clinical finding is worthy of further attention, and more reports of cases of injuries to the occipital lobe with examination after a considerable period has elapsed would help in clarifying the problem. World War II has provided numerous well documented cases of survival of injuries to the occipital lobe; these afford an unusual opportunity for further study of the effect of occipital lesions on the optic nerves.

SUMMARY AND CONCLUSIONS

A case of a veteran who sustained a severe gunshot wound to both occipital lobes in 1943 and who first showed mild primary optic nerve atrophy bilaterally only three and one-half years later is presented. The severe primary optic nerve atrophy was evident on examination five and one-half years after the injury. Transsynaptic degeneration as an explanation of these observations is discussed. From a review of the literature, it is apparent that transsynaptic degeneration in the visual system following injury to the occipital lobes has not been well established. There is some evidence, both experimental and clinical, for degeneration in the optic nerves following occipital injury, and our case is presented as a contribution to this aspect of the problem.

17. Rea, R. L.: Neuro-Ophthalmology, ed. 2, St. Louis, C. V. Mosby Company, 1941, p. 416.

ASTROCYTOMAS OF THE CEREBELLUM

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SINCE Cushing's exhaustive report in 1931,[1] little has been added to his analysis of the pathologic anatomy and treatment of astrocytomas of the cerebellum. Several authors have stated the opinion that an astrocytoma in this location is an entity among gliomas because these lesions occur most frequently in children, have an unusually long life history and demonstrate a strong tendency to formation of cysts, differing in these main respects from supratentorial astrocytomas.[2] Cushing [3] expressed the belief that because of these differences the cerebral astrocytomas should be scrutinized more carefully, but he certainly did not consider the astrocytomas located in the cerebellum and those situated in the cerebral hemispheres as separate subgroups of the gliomas. However, there must undoubtedly be a reason that these astrocytomas, differing only in locale, have strikingly different life histories, even though in most respects they are histologically the same tumor. It is our opinion that recent studies of astrocytomas and the introduction of a new classification of gliomas give a logical explanation of the apparent discrepancies in the behavior of these tumors.[4]

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Abstract of a portion of a thesis submitted by Dr. Mabon to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Cushing, H.: Experiences with the Cerebellar Astrocytomas: A Critical Review of 76 Cases, Surg., Gynec. & Obst. **52**:129-204 (Feb.) 1931.

2. Scherer, H. J.: A Critical Review: The Pathology of Cerebral Gliomas, J. Neurol. & Psychiat. **3**:147-177 (April) 1940.

3. Cushing, H.: Intracranial Tumours: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

4. (*a*) Kernohan, J. W.; Mabon, R. F.; Svien, H. J., and Adson, A. W.: A Simplified Classification of the Gliomas, Proc. Staff Meet., Mayo Clin. **24**:71-75 (Feb. 2) 1949. (*b*) Svien, H. J.; Mabon, R. F.; Kernohan, J. W., and Adson, A. W.: Astrocytomas, ibid. **24**:54-64 (Feb. 2) 1949; (*c*) A Simplified Classification of the Gliomas Based on the Concept of Anaplasia, S. Clin. North America **29**:1169-1187 (Aug.) 1949.

MATERIAL AND METHODS

This study is a review of all the verified cases of astrocytoma of the cerebellum encountered at the Mayo Clinic from 1915 to 1945 inclusive. The cases have been analyzed primarily from a surgical and a pathologic point of view. From the necropsy records and operative specimens at the clinic, 131 cases of this tumor have been collected and studied.

In every case initial microscopic examination of the operative specimen was performed at the time of operation, frozen sections being stained by the polychrome methylene blue technic. Fixed specimens were stained routinely with hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, the Mallory-Heidenhain method and, when possible, the Cajal gold chloride-mercury bichloride method. Other special stains were used when indicated.

CLASSIFICATION AND HISTORICAL BACKGROUND

Tumors of gliomatous nature were recognized macroscopically early in the nineteenth century. According to Scherer,[2] Abernethy, in 1804, designated them as "medullary sarcoma." They were described by the terms *encephaloides* by the French and *fungös medullar* by the German authors. However, it was not until the time of Virchow [5] that these tumors began to assume their identity. Virchow coined the term "glioma" and created the subgroups myxoglioma and fibroglioma, or glioma durum. The former class probably corresponded to what is now commonly spoken of as protoplasmic astrocytoma, oligodendroglioma, and so forth, and the latter, to the tumor now known as fibrillary astrocytoma, and possibly some ependymomas.

Virchow also spoke of sarcoma of the brain, and his description of this type of tumor corresponds to that of glioblastoma multiforme. However, he was necessarily handicapped by the lack of specific stains and microscopic technic and depended mostly on gross characteristics. Bailey [6] credited Golgi, in 1875, as being the first to insist that the diagnosis of glioma should be dependent on the presence of star-shaped cells. Except for some of the more recent subdivisions, such as oligodendroglioma, ependymoma and medulloblastoma, this cell is still considered omnipresent in typical gliomas.

From time to time at the turn of the century further information descriptive of these tumors was added to the literature. In 1918, Ribbert,[7] in a further elaboration of Cohnheim's theory of misplaced, incompletely differentiated (embryonal) cell rests, gave impetus to further analysis of the cellular origin of gliomas. In the same year Strauss

5. Virchow: Cited by Scherer.[2]

6. Bailey, P.: Cellular Types in Primary Tumors of the Brain, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 905-951.

7. Ribbert, H.: Ueber das Spongioblastom und das Gliom, Virchows Arch. f. path. Anat. **225**:195-213 (Aug.) 1918.

and Globus [8] formulated a histogenetic scheme to describe the various stages in the development of cellular components of the central nervous system and the tumor groups derived from these histogenetic elements. In 1925 the same authors [9] further elaborated this system of classification.

These various schemes culminated in the classic work of Bailey and Cushing,[10] in 1926. This presentation has stood the test of time and has given tremendous impetus to the advancement and study of the closely related systems of neuropathology and neurologic surgery. However, since the early introduction of this classification, many and various criticisms have justifiably been leveled at this histogenetic basis of taxonomy.

Among the discrepancies found in this concept was the place the two tumors astroblastoma and glioblastoma multiforme should properly occupy in the histogenetic scheme. The astroblastoma was so designated by Bailey and Cushing.[10] They included tumors in this category which were almost exclusively composed of cells resembling the primitive astroblast, for the most part founding their classification on the architectural arrangement of the cells. Later Bailey [6] and Bailey and Bucy [11] spoke of the astroblastoma as a type of tumor midway between the glioblastoma multiforme and the protoplasmic astrocytoma, in both of which tumors astroblasts could be seen. This transitional tendency applied not only to the histologic picture but also to the preoperative duration of symptoms and the postoperative survival period associated with the tumors. Elvidge and associates [12] also stated that the astroblastoma might be as benign as the astrocytoma or as malignant as the glioblastoma multiforme. Cushing,[1] too, spoke of the ease with which the astroblastoma is sometimes confused with glioblastoma multiforme. Recent investigation of the astroblastoma has tended to confirm the impression that this tumor has occupied an uncertain position in all former classifications, and it is now known on the basis of dedifferentia-

8. Strauss, I., and Globus, J. H.: Spongioblastoma with Unusually Rapid Growth Following Decompression, Bull. Neurol. Inst. New York **1**:273-281, 1918.

9. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme: A Primary Malignant Form of Brain Neoplasm; Its Clinical and Anatomic Features, Arch. Neurol. & Psychiat. **14**:139-191 (Aug.) 1925.

10. Bailey, P., and Cushing, H. C.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

11. Bailey, P., and Bucy, P. C.: Astroblastomas of the Brain, Acta psychiat. et neurol. **5**:439-461, 1930.

12. Elvidge, A.; Penfield, W., and Cone, W.: The Gliomas of the Central Nervous System: A Study of 210 Verified Cases, A. Research Nerv. & Ment. Dis., Proc. **16**:107-181, 1937.

tion and anaplasia, rather than of histogenesis, that it is a more malignant variant of the relatively benign tumor astrocytoma.

Glioblastoma multiforme also has fitted poorly into any histogenetic classification. It has been designated as "spongioblastoma multiforme," [13] a term earlier introduced by Globus and Strauss, but in later years it has been universally called "glioblastoma multiforme," so as to avoid confusion with the tumor spongioblastoma polare. The glioblastoma multiforme reproduces the primitive spongioblast in caricature only, and from recent studies it can logically be assumed to be a still more malignant form of astrocytoma than is the astroblastoma.[4b,c]

On the basis of grading astrocytomas from 1 to 4, it is apparent almost immediately that the fundamental difference often noted between the life history of the cerebellar astrocytoma and the cerebral astrocytoma is perhaps only one of degree of malignancy. With the system of grading mentioned, this difference can be explained by the fact that the majority of astrocytomas occurring in the cerebellum are of grade 1 malignancy, whereas one encounters in greater numbers the more malignant grades of astrocytomas above the tentorium. With respect to the life history and clinical course of the two groups, it is found that the tumors of the same grade tally closely. Thus, the only actual difference is that the tumors found in the cerebellum are much more frequently of a lower grade of malignancy than are their cerebral kin.

INCIDENCE

Age.—In our series of cases of astrocytomas of the cerebellum, the average age of the patients on admission was 13.6 years; this is in close agreement with Cushing's [1] figure of 13 years. The youngest patient was 16 months and the oldest 50 years of age.

Sex.—About equal numbers of males and of females were affected: 68 males and 63 females. Ninety-five (73 per cent) of the total series of 131 patients were 16 years old or less. In this particular group there were 47 males and 48 females.

Location.—The recorded position of the tumor was that noted at operation or necropsy. A great number of the lesions may originate from the midline and grow laterally, but only those the bulk of which was situated in either hemisphere were designated as being in this location. An analysis was made of 130 cases in our series because in 1 case generalized involvement of the arachnoid covering both hemispheres was found and in this case the question arose as to the exact site of origin of the lesion. In 67 (51.5 per cent) of the 130 cases, the lesions were

13. Cushing.[8] Bailey.[6] Bailey and Cushing.[10] Bailey, P.: Further Remarks Concerning Tumors of the Glioma Group, Bull. Johns Hopkins Hosp. **40**:354-389, 1927.

in the midline, either in the region of the vermis or in the fourth ventricle. In 40 cases the lesion occurred in the right cerebellar hemisphere, and in 23, in the left cerebellar hemisphere.

Elvidge and his associates [12] found a notable difference in the average age of patients with tumors in the hemispheres and that of patients whose lesions were located more medially, the former being considerably older. Bucy and Gustafson [14] stated that they found no such difference. In our series the average age of patients with tumors in the midline was 12.8 years, whereas that of patients with lesions more laterally placed was 14.2 years. The ranges of the youngest and the oldest were the same for the two groups.

On comparison of the locations of the cystic and the solid tumors, it was found that most of the cystic tumors were located in the hemis-

TABLE 1.—*Solid and Cystic Tumors: Location and Incidence of Nodules in 129 Cases**

Location	Solid Tumors	Cystic Tumors				
		Total	Single Cysts		Multiple Cysts	
			Without Nodules	With Nodules	Without Nodules	With Nodules
Right hemisphere	5	35	13	15	5	2
Left hemisphere	5*	17*	9	7	1	0
Total for hemispheres	10 (23.3%)	52 (60.5%)				
Midline	33 (76.7%)	34 (39.5%)	16	12	5	1
Total	43	86	38	34	11	3

* Of the 131 tumors studied, 2 were not included in the table. One tumor was located in the left hemisphere, but whether it was cystic or solid could not be determined. The other tumor was described as a generalized meningeal gliomatosis.

pheres while an overwhelming majority of the solid variety occupied more median positions (table 1).

Of the total series of 131 cases, 129 were analyzed from the standpoint of the cystic or noncystic character of the lesion. In 1 instance, the earliest in the series, operation was not performed, and the patient died elsewhere. When the sections were forwarded to the clinic for examination, no statement was made as to whether the tumor was cystic or solid. In another case the condition was described as generalized meningeal gliomatosis, as mentioned elsewhere.

Of the total number of cysts in the series of astrocytomas, 72 were single and 14 multiple. Table 1 shows the number of cystic tumors, the location of the tumors and the incidence of tumor nodules. From an analysis of table 1, it is readily seen that more than 50 per cent of the

14. Bucy, P. C., and Gustafson, W. A.: Structure, Nature and Classification of Cerebellar Astrocytomas, Am. J. Cancer **35**:327-353 (March) 1939.

cysts were without a nodule. This observation brings up the question of whether or not the tumor nodule is the main evolutionary factor in the formation of the cyst.

THEORIES OF CYST FORMATION

For some time the prevalent theory concerning the formation of these cysts has been that proposed by Cushing.[1] It was his theory that the cyst was formed by trapped fluid which had the characteristics of a transudate; the fluid originated from the tumor nodule commonly encountered within the cyst. The wall of the cystic lesion was in most instances an impermeable membrane formed by compressed cerebellar tissue. Elvidge and associates [12] suggested that both the intraneoplastic and the extraneoplastic cysts arise for the most part from liquefaction of the tumor tissue. Bucy and Gustafson [14] vigorously opposed this theory of formation of large cysts with tumor nodules, although they did agree that this process might occur in small, intraneoplastic cysts. It seemed unlikely to them that after a cyst was tapped and the fluid drained the tumor could grow and liquefy again soon enough to account for the rapid reaccumulation of fluid.

It is likely that both theories are correct and that the fluid is formed in some instances by the transudate from the tumor nubbin and at other times by necrosis and liquefaction of tumor tissue or by a combination of these two processes. However, in our series, it was difficult to assume that in the majority of cases the tumor nodule accounted for the formation of the fluid when in at least one-half the cases the tumor nodule was not demonstrable. The question might arise as to whether the nodule was always uncovered or visualized. Since it was shown that these lesions could be eradicated for indefinite periods, if not permanently, by removal of the mural nodule, it has been the practice at the clinic to search diligently for a nodule whenever a cystic lesion is encountered and to remove the nodule entirely if possible. In those instances in which a nodule is not apparent, multiple biopsies of the wall of the cyst are made to determine whether or not the wall is composed of tumor tissue. In many cases in our series in which a tumor nodule was not found, the wall of the cyst was observed to be made up of neoplastic cells. In these instances radical or, if this was not feasible, subtotal removal of the cyst was done. Of course, it is possible that occasionally in case of an unverified cystic tumor a nodule is present which forms a part of the wall but lies outside the tumor and is not visible at operation.

Concerning the undoubted predilection of a cystic tumor for location in one of the hemispheres, an adequate explanation cannot be offered. It would seem from any analysis of the figures in table 1 that the role of the tumor in producing the cystic accumulation of fluid is of less

importance than has been realized since a majority of the cystic lesions did not have a tumor nodule. But if cavitation within a tumor with resultant necrosis and liquefaction accounts for cystic tumors, why should the majority be located laterally? It might be suggested that the blood supply to the vermis cerebelli and adjacent structures is richer than that of the hemispheres; this poorer vascularity might hasten and promote cystic degeneration. The most likely explanation is that a midline tumor may give signs sooner than a tumor located in either hemisphere and thus lead to earlier diagnosis and operation, before cystic formation has begun.

In isolated cases it is even possible that the tumor may absorb completely, literally burning itself out. Cushing [1] had 2 cases in which this process may have occurred, leaving only a skeletal wall without demonstrable tumor tissue. The relative slow growth and benignity of these tumors, with their lack of invasiveness, may indicate that this type of life cycle could occur in many cases if the size of the tumor did not compromise the function of adjacent structures or interfere with the vital processes of the brain stem.

MULTIPLE TUMORS

In our series only 1 instance of multiple tumors was encountered. The patient, aged 45, had all the signs of a tumor in the left cerebellopontile angle. Suboccipital craniotomy was carried out, with intracapsular removal of a typical neurinoma of the eighth cranial nerve. During this procedure no evidence of any other tumor was noted. The immediate postoperative course was stormy, and the patient died on the second day after operation. Subsequent examination revealed a large cystic astrocytoma within the vermis cerebelli. This case has been reported in greater detail elsewhere.[15]

ROENTGENOLOGIC ASPECTS

The number of cases in our series in which calcium was noted within the tumor was small in comparison with that of other intracranial neoplasms, for example, oligodendrogliomas. Roentgenologically, 11 tumors in our series (8.5 per cent) showed evidence of calcium. It might be worth while to mention at this point that of the 129 cases which were analyzed, definite calcification, but in smaller amounts, was demonstrable microscopically in 21 (16.3 per cent), approximately twice the incidence found by roentgenographic examination. Cushing [1] reported only 1 case in which evidence of calcium was noted roentgenographically

15. Baker, G. S.; Adson, A. W., and Kernohan, J. W.: Acoustic Neurofibroma of Dumb-Bell Type Associated with Astrocytoma of Fourth Ventricle: Report of Case, Proc. Staff Meet., Mayo Clin. **15**:539-544 (Aug. 21) 1940.

but stated that the incidence was higher on microscopic examination. He did not report the number of cases included in the latter group.

In addition to the usual roentgenographic variations noted in association with tumors of the posterior fossa in persons who are in the first or second decade of life, such as secondary pressure erosion of the posterior clinoid processes, increased convolutional markings and separation of the suture lines, more localizing roentgenographic signs occasionally are found. Thinning of the skull overlying the cerebellar hemispheres was noted on preoperative roentgenographic study in 3 instances.

In only 1 of the entire series of cases was the pineal gland observed to be definitely shifted upward. The relative rarity of this observation in this series can be explained by the infrequent calcification of the pineal gland among patients less than 20 years of age.[16] Although an upward displacement of the pineal gland is more frequently encountered, some authors report that posterior displacement of the pineal gland in subtentorial tumors is common. Hawes and Mead[17] cited 3 instances in which the pineal body was displaced posteriorly. They stated the belief that this finding could be explained by enlargement of the third ventricle, produced by blocking of the fourth ventricle or aqueduct, with resultant backward encroachment on the gland.

PATHOLOGIC ASPECTS

Gross Appearance.—At operation the tumor may be quite apparent lying on the surface of either hemisphere or the vermis, but oftenest it is located deep within the substance of the cerebellum. If the tumor is a surface lesion and presents medially, it may be seen through the transparent arachnoid on reflection of the dura over the cisterna cerebellomedullaris.

The vermis should be carefully inspected for broadening and widening of the folia and convolutions. However, when the tumor is laterally located deep within the hemisphere, there may be a telltale enlargement of the affected lobe, as well as a difference in the size of the surface markings.

If there are no alterations in the surface markings, a cannula may be introduced into the hemisphere suspected on the basis of clinical features of harboring the lesion; if a cystic tumor is present, varying amounts and shades of xanthochromic fluid will be obtained. This fluid usually coagulates spontaneously on being exposed to the air for a few minutes because of its high protein content, but occasionally this will not occur. In our series, 86 (66.7 per cent) of the astrocytomas

16. Vastine, J. H., and Kinney, K. K.: The Pineal Shadow as an Aid in Localization of Brain Tumors, Am. J. Roentgenol. **17**:320-324 (March) 1927.

17. Hawes, L. E., and Mead, S.: Posterior Displacement of the Calcified Pineal in Subtentorial Brain Tumors, Radiology **40**:367-370 (April) 1943.

were cystic. The contents of these cysts varied in quantity from a fraction of an ounce to as much as 3 ounces (90 cc.), the latter amount occurring in several instances.

On uncapping the cavity, one can see the glistening white walls, usually made up of compressed normal cerebellar tissue. Occasionally, however, the wall may be partially, if not entirely, composed of tumor tissue. There may be either single or multiple cysts. The former predominated in our series, there being 72 single and 14 multiple cysts.

If a mural nodule is present, it is usually grayish pink and varies in size from a fraction of a centimeter to as large as 4.5 cm. in diameter.

Not infrequently the tumor may be solid, as in 43 cases, or 33.3 per cent of the cases of astrocytoma in our series, and, once again, it is well to mention that the noncystic lesions have a predilection for being medially placed (76.7 per cent). When solid, and not deeply embedded within the cerebellar substance, the tumor may present itself as a grayish pink, friable mass in the midline, closely resembling a medulloblastoma, or even suggesting an ependymoma. On occasion, however, it may be rather firm and rubbery.

In passing, an interesting case should be mentioned. In this instance, curiously, a large cystic tumor of the vermis and left cerebellar hemisphere had grown through the superior surface of the cerebellum and had invaded the subarachnoid space beneath the tentorium. No other implants were observed in the subarachnoid space or on the ventricular walls.

Microscopic Appearance.—As mentioned earlier, by far the majority of astrocytomas occurring in the cerebellum are of grade 1. Of a total of 131 cerebellar astrocytomas, 109 were of grade 1, 14 of grade 2 and 8 of grade 3. There were no tumors of grade 4 in our series.

The criteria for classification of the cerebellar astrocytomas according to the various grades of malignancy on the basis of dedifferentiation and anaplasia are the same as have been outlined in detail elsewhere for astrocytomas occurring in the cerebral hemispheres.[4b, c] However, a brief review of the various microscopic factors on which the system of grading is based follows.

Grade 1: These tumefactions consist of astrocytes which are normal in appearance. However, the normal cerebellar architecture is destroyed in the immediate locale of the tumor. In contradistinction to cerebral astrocytomas, the majority of astrocytomas occurring in the cerebellum are cystic, and consequently the infiltrative, diffuse appearance seen in the supratentorial lesions is not commonly encountered in this region. Instead, the walls of the cyst or the edges of the tumor pass rather quickly into normal cerebellar tissue, or perhaps the walls may be composed of cerebellar tissue which has lost its normal architecture as a result of compression by the enlarging cyst. However, in the solid

tumors the same wide zone of transition from tumor to normal cerebellar tissue may be seen as in the solider cerebral astrocytomas. Most of the astrocytes are fibrillary, with the small cell body and myriad dense, intertwining processes forming a thick matrix. The number of fibers is apparently not dependent on the number of cells actually present, because in some instances in which there were few cell bodies the tumor had an extremely matted appearance.

The nuclei are generally eccentrically placed and may contain chromatin granules or masses. The cell body may be difficult to visualize, but generally the fibrillary processes, particularly with Cajal's special stain, are easily seen. Only occasionally will the stain prove good enough for visualization of the neuroglial fibers coursing through the cytoplasm.

The tumors are relatively avascular, although occasionally one has an unusually rich blood supply. In rare cases the vessels may have intimal proliferation, or "budding," with partial obliteration of the lumen. These lesions contain little connective tissue, and it is wholly confined to the thin-walled vessels.

The myelin sheaths of the nerve fibers are commonly altered, whereas the axis-cylinders seem to be considerably hardier and, although greatly distorted, often persist as apparently functioning units deep within the tumor. Ganglion cells are less resistant and are rarely seen within or near the outer boundaries of the growth.

Degeneration is encountered in some instances, but there is still a definite attempt at organization, in contradistinction to the widely disorganized appearance of the more malignant varieties. Considerable intercellular edema often is present in regions within the tumor. This may account in part for the formation of cysts, for by increasing pressure the edematous areas could slowly throttle the already scanty blood supply and thus further the eventual breakdown of the tumor. Other constituents may be present which are commonly observed in non-neoplastic, as well as neoplastic, degeneration. They are the dark, homogeneously staining, club-shaped bodies which Verhoeff [18] termed "cytoid bodies" and the "Rosenthal fibers" described by Liber [19] (fig. 1).

As mentioned elsewhere, calcification was noted microscopically in 21 cases (16.3 per cent). Deposits of calcium may be laid down as concentric rings of bluish violet, pleomorphic calcospheres, irregularly shaped, but there was no evidence from our study that the deposition was primarily in the walls of the blood vessels. Calcification is frequently a concomitant of degeneration, but it is not correct to assume that it is

18. Verhoeff, F. H.: Tumors of the Optic Nerve, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 1029-1039.

19. Liber, A. F.: The Nature of Rosenthal Fibers, J. Nerv. & Ment. Dis. **85**:286-304 (March) 1937.

always characteristically associated with slowly growing tumors. For some reason, it seems to be intimately interwoven with tumor metabolism, for even in some rather rapidly growing neoplasms it may be observed in abundance. Admittedly, it usually occurs to a greater extent in the more slowly growing neoplasms, but why it should be encountered to such an overwhelmingly greater degree in oligodendrogliomas than in astrocytomas, when the average postoperative period of survival for several series of patients with astrocytomas was ten to twenty months longer than for patients having oligodendrogliomas, is difficult to explain. Elvidge and associates [13] observed mitotic figures in all oligodendro-

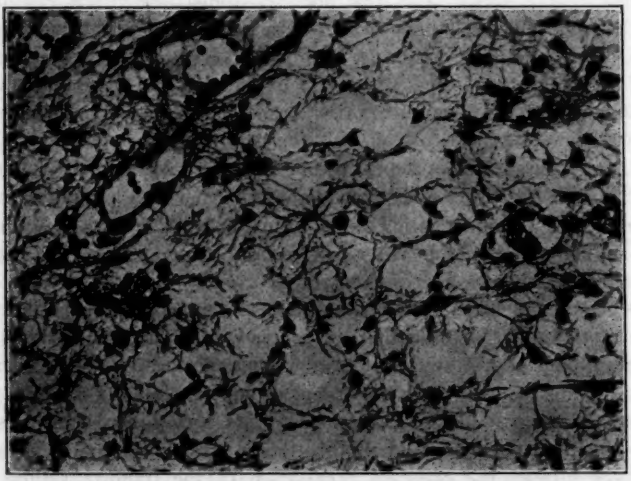

Fig. 1.—Astrocytoma grade 1. The uniformity of structure is evident. All the cells appear to be normal astrocytes. Hematoxylin and eosin stain; × 295.

gliomas in their series of cases and stated that calcareous deposits may occur even in the presence of rapid growth.

Dedifferentiation, as commonly indicated by pleomorphism, hyperchromatism of cytoplasm and nucleus and mitotic figures, is not observed in these tumors.

Grade 2: The greater degree of malignancy of tumors of this grade is indicated by the changes commensurate with early anaplastic transformation. Most of the astrocytes are normal in appearance, but there is a slight pleomorphism of both cytoplasm and nucleus with hyperchromatism. Mitotic figures are not visible.

The vascularity of the tumors varies, but in the majority of cases the blood supply is abundant. Endothelial and adventitial budding of the

walls of the vessels occur, but the latter seems to predominate. Cystic areas and regions of degeneration are common. The connective tissue stroma is scanty and is found in close approximation to the vascular tree.

Little encapsulation occurs, although the line of demarcation between normal and tumor tissue is more readily apparent macroscopically than in the neoplasms of grade 1 (fig. 2).

Grade 3: As mentioned elsewhere,[4b, c] the majority of the cells are readily identified as variants of astrocytes. Cellularity is greater, and the cells vary to a rather striking degree in size and shape. Anaplastic transformation is commonly encountered, and cells showing pleomorphism and hyperchromatism of cytoplasm and nucleus are widely distributed.

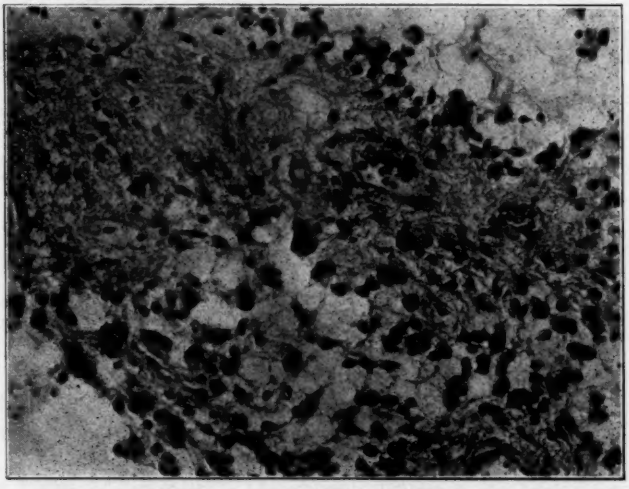

Fig. 2.—Astrocytoma grade 2. Evidence of beginning anaplasia is present. The majority of cells appear to be normal astrocytes. The remaining cells are pleomorphic, and their nuclei are hyperchromatic. No mitotic figures are present. Hematoxylin and eosin stain; × 295.

Mitotic figures are present, averaging at least one in every other high power field.

Changes in the blood vessels are encountered rather frequently. Endothelial and adventitial proliferation is common, the former predominating. Often the lumen is narrowed, and in some instances it may be occluded. This in part may account for the increased tendency toward necrosis and degeneration.

The transitional zone between normal cortical and subcortical tissue and neoplastic tissue is sharply delimited macroscopically, as well as microscopically (fig. 3).

Grade 4: Astrocytomas of grade 4 were not found in our series. We did note, however, particularly in the astrocytomas of the two lower grades of malignancy, perivascular arrangement of cells, piriform with vascular feet and fine antipodal processes radiating from the body proper. This perivascular actiniform arrangement was rare in the tumors of grade 3.

In the entire series there was only 1 verified instance of meningeal gliomatosis. In this case the tumor at operation presented a picture of chronic exudative arachnoiditis with the arachnoid bound down to both cerebellar hemispheres, the vermis and the medulla. The entire process, according to the surgeon, was so vascular that any attempt at radical

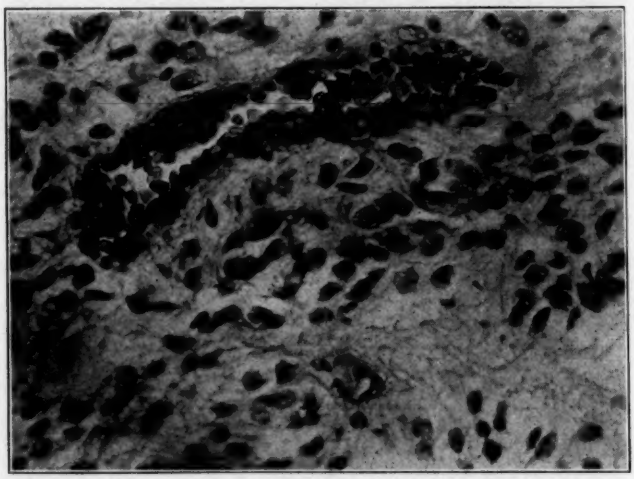

Fig. 3.—Astrocytoma grade 3. Evidence of moderate anaplasia is present. About one-half the cells appear to be normal astrocytes; the remaining half are pleomorphic, and their nuclei are hyperchromatic. Mitotic figures are present, averaging one in every other high power field. Hematoxylin and eosin stain; × 455.

removal was obviously impossible. The patient died two years later, but, unfortunately, postmortem examination was not made; consequently, detailed study of the spinal cord for implants was not carried out. No instance of implants in the cord was found in this series. This is in contrast to experience with the other tumors occurring in this region, for example, the medulloblastomas, which make up 47.6 per cent of all cases of meningeal gliomatosis.[20]

20. Polmeteer, F. E., and Kernohan, J. W.: Meningeal Gliomatosis: A Study of 42 Cases, Arch. Neurol. & Psychiat. **57**:593-616 (May) 1947.

PREOPERATIVE DURATION OF SYMPTOMS AND POSTOPERATIVE SURVIVAL

An analysis of cases in which satisfactory follow-up records were available for patients who had survived operation longer than one month is presented in table 2.

In 2 cases an astrocytoma of grade 3 was totally extirpated by the surgeon so far as he could tell at the time of the procedure; if these cases are eliminated, the average postoperative survival period was three months. Obviously, the number of tumors of both grades 2 and 3 is too small to make any satisfactory comparison with the tumors of grade 1. As mentioned earlier, the survival period of patients having cerebellar tumors of grade 1 compares favorably with the survival period of patients having astrocytomas of grade 1 occurring above the tentorium.

The fact that an overwhelming majority of the cerebellar astrocytomas are of grade 1 accounts for the seeming disparity in the survival rate

TABLE 2.—*Average Preoperative Duration of Symptoms and Postoperative Survival of Patients Having Astrocytomas*

Number of Patients	Grade of Tumor Malignancy	Average Preoperative Duration of Symptoms (Months)	Average Postoperative Survival (Months)
109	1	13.9	78.0
14	2	11.7	74.6
8	3	8.5	84.0
0	4	....	....

between the astrocytomas occurring in the cerebellum and those occurring in the cerebrum. Among the latter there are more tumors of the higher grades of malignancy.

The postoperative survival period of patients having solid tumors grade 1 was 77.5 months. The patients having cystic tumors grade 1 survived an average of 81.4 months. Those with nodules survived an average of 86.3 months after operation, and those without nodules survived 76.6 months after operation. As mentioned elsewhere, 2 tumors were not included in this analysis of cystic and solid tumors.

It is apparent that little difference exists in the survival period of patients having cystic and solid tumors and that, although the difference is slight, cystic tumors with nodules have a slightly better prognosis than those without nodules. This may be due to more radical attempts at eradication if a tumor nodule is uncovered.

SUMMARY AND CONCLUSIONS

In our study, 131 astrocytomas of the cerebellum encountered at the Mayo Clinic from 1915 to 1945 inclusive were reviewed. These tumors were graded on the basis of malignancy, that is, by the degree of dedif-

ferentiation and anaplasia, from 1 to 4. It was found that an overwhelming majority (83 per cent) were of grade 1. This accounts for the apparent difference other observers have noted between supratentorial and cerebellar astrocytomas, that is, that the latter are apparently more benign. With respect to preoperative duration of symptoms and postoperative survival period of the patient, a comparison of the life history of tumors of grade 1 occurring above the tentorium with that of tumors of the same grade occurring below the tentorium shows no difference between the tumors. The only real dissimilarity is the fact that astrocytomas of grade 1 occur more frequently in the cerebellum than do the more malignant varieties.

In our series 51.5 per cent of the 130 tumors were observed lying in the midline. There were twice as many cystic as solid tumors. Of the cystic tumors, the majority (60.5 per cent) were in a hemisphere, whereas of the solid tumors 76.7 per cent were predominantly in the midline. A few more than one-half the cystic tumors were without nodules.

It is possible that cysts may be formed by a transudate from a mural nodule, as well as by liquefaction of tumor tissue. However, the importance of the former factor may have been overemphasized. Cysts may seem to occur laterally oftener than medially if they are a result of slow breakdown of tissue, because a midline tumor may give rise to symptoms sooner, thus leading to earlier diagnosis and treatment.

In only 1 case in the entire series was there meningeal gliomatosis.

The prognosis is relatively unaffected by the cystic or noncystic character of the lesion.

ISOLATED NEURITIS OF A SENSORY FILAMENT OF A PERIPHERAL NERVE TRUNK

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THE OBSERVATION to be described is of interest to the physician in general practice, to whom the sufferer appeals first. The condition is frequently misleading with respect to its localization, cause and prolonged course, all leading to erroneous therapeutic measures. Because of its comparative infrequency and the beneficial results obtained from a special method of treatment, the presentation of the subject is warranted.

The peripheral nerve trunks of the extremities, being composed of mixed motor and sensory fibers, when in a state of irritation or inflammation will give rise to both motor and sensory phenomena. This is a common observation. Isolated involvement of either motor or sensory nerve fibers is sometimes observed. The physician is familiar with motor neuritis and sensory neuritis. For example, in multiple neuritis caused by lead intoxication, motor phenomena (paralyses) are almost exclusively present and the sensory disturbances are usually absent. In syphilis multiple sensory neuritis may alone be present for a long time. Alcoholic neuritis may also be exclusively sensory.

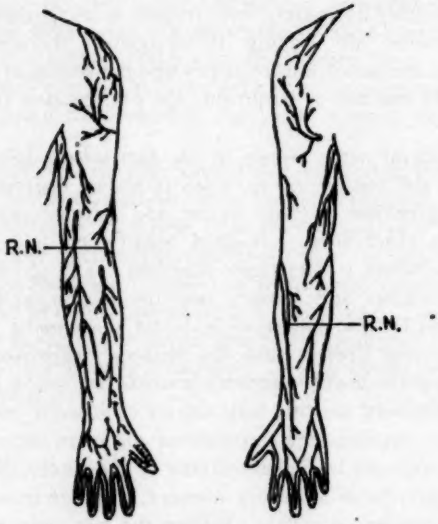
When one considers the branches of the main nerve trunks of the extremities, paralyses or inflammations of the motor divisions are not unusual, but neuritis of a sensory filament, to judge from the neurologic literature, is certainly a rarity. Within the last eight months, 4 cases have come under my observation, all presenting a singular similarity in the localization, as well as in subjective and objective manifestations, pointing to involvement of the inferior branch of the external cutaneous branch of the radial (musculospiral) nerve. The absence of any record of such a case in the literature at my disposal warrants the publication of my observations.

REPORT OF CASES

Of the 4 patients, 2 were men and 2 women. Three were of middle age, and 1 (a woman) was 23 years of age. One man was a barber; the other, a cutter (tailor), and the 2 women did housework. None but the young woman used alcohol, but she used it freely.

On first consulting me, all the patients complained of a pain immediately behind the lateral epicondyle of the right arm. Curiously, in each of them the right arm

was involved. When the forearm was in pronation there was no pain, but as soon as slight pressure was made over the painful spot, at a distance of ½ inch (1.3 cm.) above or below it, the pain was exquisite. The epicondyle itself was not tender. Spontaneous or induced movements of the forearm, unless they were violent, were all painless, except for supination, which in 3 cases was slightly painful and in 1 not at all painful. The barber, in particular, stated that each time that he had to turn the hand in an outward movement, in shaving or in cutting hair, pain would appear in the area mentioned, so that he was obliged to discontinue his work for a few moments. In addition to the pain brought on by pressure or by certain movements, there was also spontaneous pain behind the lateral epicondyle and radiating down the posterior aspect of the forearm or its middle and external sides for a distance of one-third the length of the limb. This pain was paroxysmal,



Innervation of the arm: posterior aspect at left; anterior aspect at right. *R.N.* indicates the inferior external cutaneous branch of the radial (musculospiralis) nerve.

came on even when the arm was at rest and had the character of a neuralgic pain; that is, it appeared suddenly, without any apparent cause, and was sharp and lancinating.

Careful examination for general sensation in the area of distribution of the lower external cutaneous branch of the radial nerve (figure) showed hyperesthesia in the 2 men and hypesthesia to touch, pain and temperature sensations in both women. As is well known the external cutaneous branch of the radial nerve (posterior cutaneous nerve of the forearm; nervus cutaneus antibrachii dorsalis) passing down between the outer and the inner head of the triceps, divides near the elbow into its upper and lower branches. The upper branch, the smaller, supplies the skin over the lower half of the outer and anterior aspect of the arm. The lower branch, the larger, runs behind the lateral epicondyle and supplies the skin of the middle of the back of the forearm, anastomosing with the medial

antibrachial cutaneous and musculocutaneous nerves. The partial preservation of sensibility in my cases over the area of distribution of the lower branch of the external cutaneous branch of the radial nerve is probably due to its anastomosis with other sensory branches, but why hyperesthesia should be present in some cases and hypesthesia in others is difficult to explain with certainty. The difference probably depends on the degree of inflammation of the nerve; with a greater degree of inflammation, hyperesthesia is likely to be present, whereas with a less degree hypesthesia is the result. This contention finds its corroboration to a certain extent in the course of the neuritis in these 4 patients. The 2 women whose affected areas were hypesthetic recovered in a comparatively short time (from two to four weeks), whereas the men with the hyperesthesia suffered from four to six months.

To summarize, the disturbance presented exclusively sensory phenomena, namely, tenderness of a sensory nerve trunk, disturbed subjective symptoms (hyperesthesia and hypesthesia) to all forms of sensation over the area of distribution of the nerve involved, and spontaneous pain of a neuralgic character, commencing immediately behind the lateral epicondyle and radiating down the back of the forearm to a certain distance. No motor phenomena could be observed in the affected area, and trophic disturbances were likewise absent. The entire pathologic picture was solely in the domain of one sensory branch of the radial nerve.

It was previously mentioned that pain could be brought on only by supination of the forearm in 3 of the cases. The reason lies probably in the fact that the brachioradialis (supinator longus) arises from the upper two thirds of the lateral supracondylar ridge of the humerus and from the lateral intermuscular septum of the arm. The lower branch of the external cutaneous branch of the radial nerve, which is involved here, also separates from its upper branch at the level of the intermuscular septum. There is consequently close proximity of the origins of the nerve and muscle; a display of the latter will irritate the nerve, which is in a state of inflammation.

The cause of this neuritis is probably that of neuritis in general. None of my patients could tell whether a trauma had been sustained or not; perhaps a slight trauma had occurred, but had passed unnoticed. Exposure to cold may have been a factor; the 2 women were obliged to do general housework; they stated that their arms were frequently in contact with cold water. Had the occupations of the men anything to do with their sensory neuritis? They said that they were obliged to discontinue their work, as the movements involved invariably caused pain. A complete rest gave entire relief. While it is easy to conceive that some stretching of tissue and of cutaneous nerves takes place when the forearm is in a state of flexion for a long time (and this is precisely the situation with barbers and cutters), it is, nevertheless, difficult to attribute the neuritis exclusively to this factor, as otherwise a sensory neuritis of the particular nerve would be a frequent occurrence, which, of course, is not the case. The 2 men patients and the middle-aged woman had

had rheumatism for years. The tailor had once had an attack of occupational cramp in the right hand. The barber had once experienced paresis of the right hand after a cold bath. The young woman was alcoholic, and perhaps syphilitic. All these predisposing factors probably played a certain role in the causation.

Bier's treatment with induced hyperemia was conspicuously beneficial in all 4 cases. Complete abstention from work and exposure and hot baths, local application, were additional measures.

1520 Spruce Street.

ELECTROMYOGRAPHY IN DIAGNOSIS OF NERVE ROOT COMPRESSION SYNDROME

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ELECTROMYOGRAPHY, long used in physiologic research, has recently emerged as a clinical diagnostic method with a high degree of accuracy and widespread clinical application. With the recent advances in electronics it is now possible to produce commercially a sensitive instrument which utilizes a needle electrode placed directly into a denervated muscle and which records characteristic action potentials by means of a cathode ray oscilloscope. Such an instrument [1] has been used in this study to determine the exact location of lesions causing compression of spinal nerve roots. This localization depends on the accurate detection of the action potentials of denervation fibrillation, whereas heretofore electromyographic localization of a lesion of a single nerve root has depended on the detection of fasciculation by the use of percutaneous electrodes, a much less accurate method (page 96).

Visible fibrillation of a denervated muscle was first described by Schiff in 1851, when he sectioned the hypoglossal nerve in dogs. Nonvisible denervation fibrillation recorded electrically (electromyography) has been studied by numerous investigators: Weddell, Feinstein and Pattle [2]; Feinstein, Pattle and Weddell [3]; Hoefer and Putnam,[4] and others. These studies led to the specific investigation with the electromyograph of lower motor neuron disease in man and in animals. Golseth

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From the Departments of Physical Medicine and Neurosurgery, Mercy Hospital.

Presented at the joint meeting of the Southern California Neurosurgical Society and the San Francisco Neurological Society, Del Monte, Calif., Feb. 26, 1949.

1. The instrument used was purchased by the Mercy Hospital from the Meditron Company, Pasadena, Calif.

2. Weddell, G.; Feinstein, B., and Pattle, R. E.: Clinical Application of Electromyography, Lancet **1**:236, 1943; The Electric Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, Brain **67**:178, 1944.

3. Feinstein, B.; Pattle, R. E., and Weddell, G.: Metabolic Factors Affecting Fibrillation in Denervated Muscle, J. Neurol., Neurosurg. & Psychiat. **8**:1, 1945.

4. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201-218 (Aug.) 1939.

and Fizzell,[5] Jasper and Johnston,[6] Jasper,[7] and Loofbourrow[8] have repeatedly demonstrated that the electromyograph can record accurately the electrical abnormalities associated with lower motor neuron disease. Its clinical use as a diagnostic aid in neurologic disorders has been emphasized by Hoefer and Guttman[9]; Brazier, Watkins and Michelsen,[10] and Huddleston and Golseth.[11]

The purpose of the present study was to determine whether or not lesions compressing a single spinal nerve root could be located exactly with the more accurate technic using the needle electrode and cathode ray oscilloscope. We have also attempted to outline a simple and precise method of identifying the specific nerve root involved. In 75 consecutive cases, the accuracy of the electronic diagnosis has been compared with that of ethyl iodophenylundecylate (pantopaque®) myelography and the results have been verified surgically.

INSTRUMENTS, MATERIAL AND METHODS

The instrument (fig. 1) used in this investigation was the Meditron model 201 clinical electromyograph. This instrument contains a high gain, low noise, balanced amplified system, driving a cathode ray oscilloscope, a power meter and a loud speaker. The amplifying system is of the differential type, providing a high degree of in-phase voltage rejection, to eliminate extraneous voltages which may be picked up from power lines and other sources of electrical interference. The oscilloscope has a maximum deflection sensitivity of 100 microvolts per inch (2.5 cm.) and a noise level of approximately 2 microvolts. The frequency response covers the range of 40 to 3,000 cycles per second. The amplification is standardized by a built-in calibrator which provides suitable voltages for checking the amplification factor at all settings of the sensitivity control. The oscilloscope sweep velocity is adjustable between the values of 10 to 1,000 milliseconds per inch and is usually operated at 20 milliseconds per inch.

5. Golseth, J. G., and Fizzell, J. A.: Electromyographic Studies on Cats After Section and Suture of the Sciatic Nerve, Am. J. Physiol. **150**:558-567, 1947.

6. Jasper, H. H., and Johnston, R. H.: A Portable Clinical Electromyograph: Report to Associate Committee on Army Medical Research, National Research Council, Canada, Montreal Neurological Institute, McGill University, 1945.

7. Jasper, H. H.: Report to Associate Committee on Army Medical Research, National Research Council, C-6239 Canada, Montreal Neurological Institute, McGill University, 1945.

8. Loofbourrow, G. N.: Electrographic Evaluation of Mechanical Response in Mammalian Skeletal Muscle in Different Conditions, J. Neurophysiol. **11**:153-167, 1948.

9. Hoefer, P. F. A., and Guttman, S. A.: Electromyography as a Method for Determination of Level of Lesions in the Spinal Cord, Arch. Neurol. & Psychiat. **51**:415-422 (May) 1944.

10. Brazier, M. A. B.; Watkins, A. L., and Michelsen, J. J.: Electromyography in Differential Diagnosis of Ruptured Cervical Disk, Arch. Neurol. & Psychiat. **56**:651-658 (Dec.) 1946.

11. Huddleston, O. L., and Golseth, J. G.: Electromyographic Studies of Paralyzed and Paretic Muscles in Anterior Poliomyelitis, Arch. Phys. Med. **29**:92-98, 1948.

The electromyogram is recorded by a synchronized camera which photographs a single oscilloscope tracing on each frame of a roll of 35 mm. film at any selected instant.

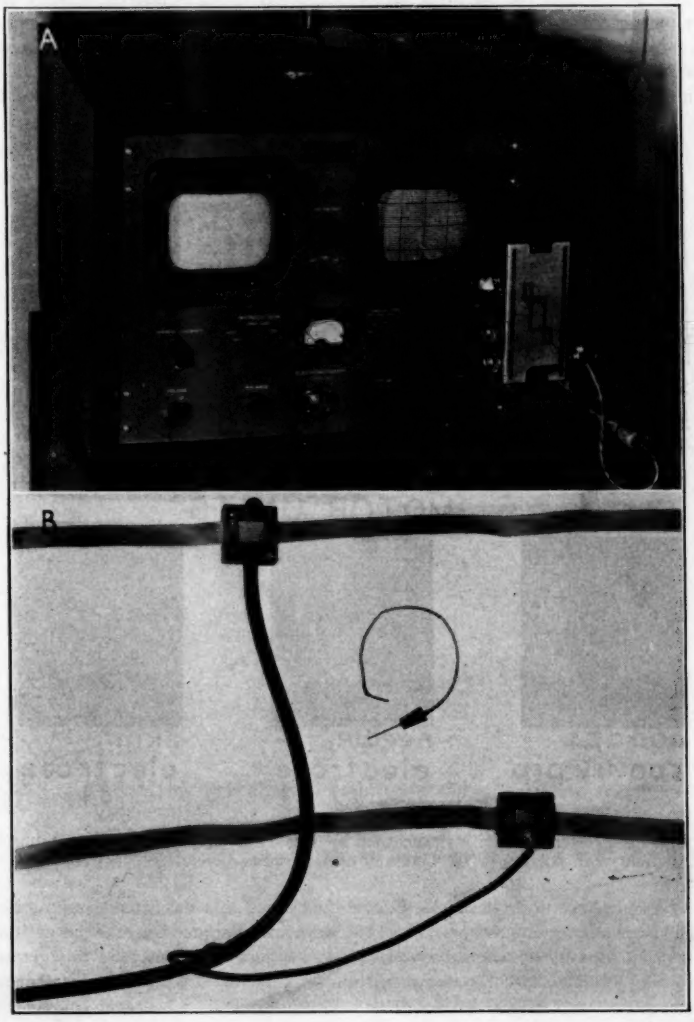

Fig. 1.—*A,* Meditron clinical electromyograph and camera; *B,* needle electrode.

All recordings were made with specially prepared needle electrodes. These are ordinary fine sewing needles from which the "gloss" has been removed with sulfuric acid. The needles are next mounted on small corks and dipped in liquid plastic

(amercoat® 3-D, clear; gentian violet is added to give color), only the tip being allowed to remain bare. This effectively insulates all of the needle except for a very small area at the tip, which then becomes the active electrode.

We believe that the use of the needle electrode, which is inserted directly into the muscle fibers to be tested, is essential for accurate electromyography, since it is virtually impossible to record denervation fibrillation without direct contact between electrode and involved muscle. Electrodes applied only to the overlying skin (percutaneous) are not sensitive to the minute action potentials caused by

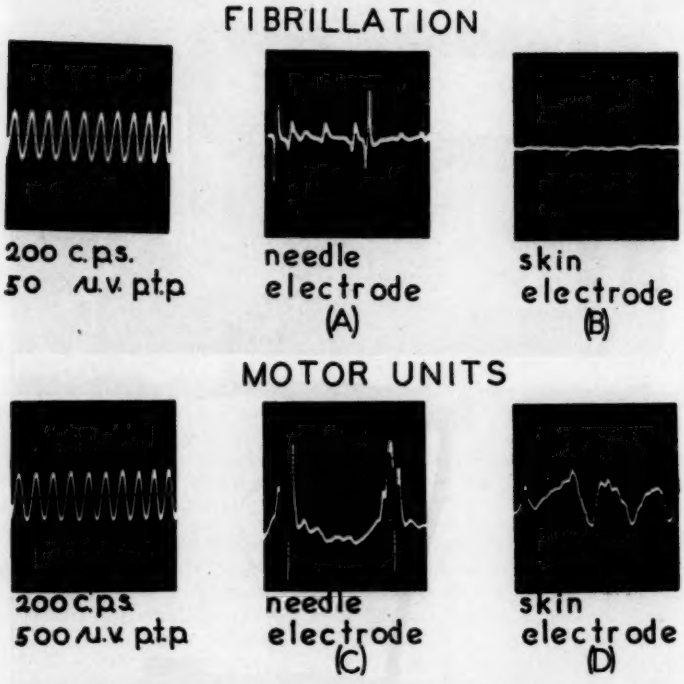

Fig. 2.—Electrical activity as recorded by needle and skin electrodes from muscle of a patient with poliomyelitis. Courtesy of Dr. James G. Golseth.

denervation fibrillation. It should also be emphasized that the cathode ray oscilloscope more accurately records these action potentials than does the ink-writing instrument used in the original investigations. Figure 2 demonstrates this greater sensitivity of intramuscular electrodes, showing the failure of the percutaneous electrode even to record the denervation action potentials.

All the examinations were conducted in a room which was completely enclosed in copper screening to prevent outside electrical interference. The room was darkened, so as better to visualize the wave forms as they flashed across the screen. A small flexible lamp was mounted above the instrument so that sample photographs could be made by means of the attached synchronized camera.

The patients were placed on an examining table in a comfortable supine position. No premedication was given. A suitable ¾ by ¾ inch (3.8 by 3.8 cm.) copper ground was attached 4 to 8 inches (10 to 20 cm.) from the area examined. The skin was next prepared over a small area with an electrode jelly, and a surface electrode was strapped in place. After the skin was prepared with an antiseptic, the needle electrode was inserted deep into the muscle to be tested and connected to the surface electrode. Recordings were obtained from several portions of the muscle being tested, to be sure that the muscle was actually denervated, for not all areas will necessarily exhibit denervation fibrillation unless all the fibers of the affected nerve root are interrupted. This information cannot be obtained by any other method.

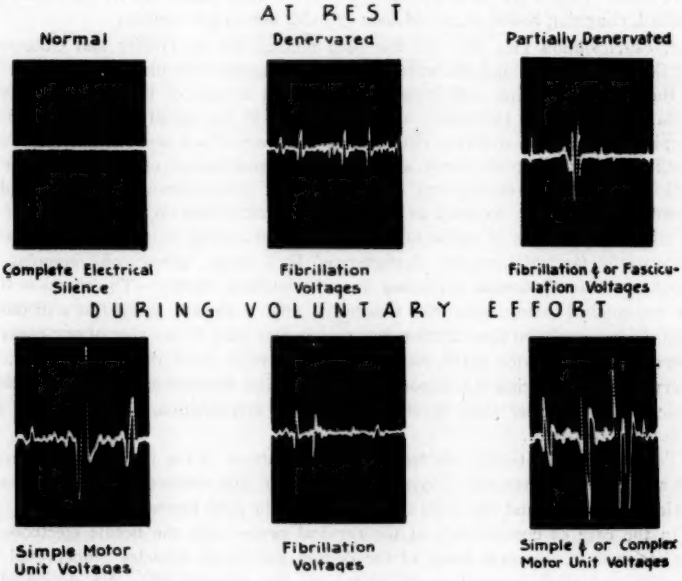

Fig. 3.—Characteristic voltages of normal and abnormal skeletal muscle. Courtesy of Dr. James G. Golseth.

The instrument records three abnormal action potentials from denervated muscle.

1. *Denervation Fibrillation* (fig. 3).—A normal muscle at rest is electrically quiet. Approximately two weeks after a nerve or nerve root has been injured or severed, a physiologic phenomenon known as fibrillation occurs in the resting muscle. These spontaneous abnormal action potentials are picked up from the denervated muscle by needle electrodes and visualized on the cathode ray oscilloscope. They appear as monophasic and diphasic spikes one to two milliseconds in duration and from 5 to 100 microvolts in amplitude. They repeat rhythmically from two to twenty times per second. In addition to the unmistakable wave forms seen on the screen, there is a characteristic high-pitched, clicking sound which is heard through a loud speaker. This sound is similar to ordinary static. These wave

forms and sounds are elicited from a resting muscle only when that muscle has sustained a lower motor neuron lesion. Denervation fibrillation does not occur with upper motor neuron lesions. This phenomenon continues as long as the muscle remains muscle (i. e., until fibrosis or fatty degeneration has occurred) or until the muscle is completely reinnervated.

2. *Complex Motor Units* (fig. 3).—With active contraction a normally innervated muscle will yield a simple diphasic wave. This apparently results from the synchronous contraction of the motor unit. A muscle in which the nerve supply is regenerating or is degenerating (as a result, for example, of pressure on an anterior nerve root by a herniated nucleus pulposus) will, on the contrary, contract in an asynchronous manner, thus producing an unmistakable polyphasic, or complex, wave form. This wave form produces a characteristic sound which resembles the strained, chugging sound of an old four cylinder automobile engine.

3. *Fasciculation* (fig. 3).—As has been pointed out by Hoefer and Guttman[9] and Brazier, Watkins and Michelsen,[10] fascicular muscle twitchings may be recorded by the electromyograph and indicate the level of lesions of the spinal cord and cauda equina. These twitchings are often visible to the naked eye but frequently are picked up by the sensitive electromyograph even if not seen clinically. There is still considerable controversy as to the exact mechanism of the production of fasciculation (Denny-Brown and Pennybacker[12]; Denny-Brown[13]) but the phenomenon is generally accepted as indicating chronic irritation or degeneration of the anterior horn cells or motor nerve roots. In the resting muscle the wave forms produced by fasciculations are characterized by a large, spontaneous, complex or polyphasic action potential, occurring in an arrhythmic manner. The sound is that of a low-pitched thump, much like that heard when a shotgun is fired at a distance. It should be noted that fasciculation was seen in less than 50 per cent of our cases of compression of anterior nerve roots, whether cervical or of the cauda equina, an observation emphasizing the importance of detecting fibrillation voltages for diagnostic purposes rather than depending solely on fasciculation, as reported in the earlier investigations.

To illustrate the typical electromyographic features of the nerve root compression syndrome, one may take 2 hypothetic cases, one with compression of the seventh cervical nerve root and one with compression of the fifth lumbar nerve root.

In the case of compression of the cervical nerve root, the needle electrode is first inserted into several areas of the deltoid and biceps muscles (innervated by the fifth and sixth cervical nerve roots) on the affected side. No denervation fibrillation, complex motor units or fasciculation is seen. The needle electrode is next placed successively in the bodies of the extensor carpi radialis, extensor communis digitorum and extensor carpi ulnaris and flexor carpi ulnaris muscles (innervated by the sixth, seventh and eighth cervical nerve roots). Here, a maximum amount of denervation fibrillation, complex motor units and possibly fasciculation is picked up. It should be noted that the flexor carpi ulnaris is tested in order to rule out a peripheral lesion involving the radial nerve. Next, the abductor digiti quinti (innervated by the eighth cervical and first thoracic nerve roots) is examined. No abnormal bioelectric impulses are elicited. Therefore the lesion is accurately localized to the seventh cervical nerve root.

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12. Denny-Brown, D., and Pennybacker, J.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311-334, 1938.

13. Denny-Brown, D.: Interpretation of the Electromyogram, Arch. Neurol. & Psychiat. **61**:99-128 (Jan.) 1949.

In the case of compression of the fifth lumbar nerve root, a similar deductive method is used. The needle electrode is first placed deep in various portions of the quadriceps femoris muscle (innervated by the second, third and fourth lumbar nerve roots). No abnormal potentials are noted. Moderate denervation fibrillation, complex motor units and possibly fasciculation are picked up from the tibialis anterior, extensor hallucis longus, peroneus longus and peroneus brevis muscles (innervated by the fourth and fifth lumbar nerve roots). Maximal abnormal responses are elicited

TABLE 1.—*Electromyographic Localization of Lesions of the Cervical Nerve Roots*

Muscles Tested	Root Innervation	Peripheral Nerve Innervation	Location of Lesion as Indicated by Degree of Denervation Fibrillation		
			C 6	C 7	C 8
Deltoideus	C 5, C 6	Axillary	+++	(—)	(—)
Biceps brachii		Musculo-cutaneous			
Triceps brachii	C 6, C 7, C 8	Radial	+	+++	+
Flexor carpi ulnaris		Ulnar			
Extensors of wrist		Radial			
Carpi radialis longus	.....	.....	.....	....	....
Carpi radialis brevis	.....	.....	.....	....	....
Digitorum communis	.....	.....	.....	....	....
Carpi ulnaris	.....	.....	.....	....	....
Abductor digiti quinti	C 8	Ulnar	(—)	(—)	+++

TABLE 2.—*Electromyographic Localization of Lesions of Lumbosacral Nerve Roots*

Muscles Tested	Root Innervation	Peripheral Nerve Innervation	Location of Lesion as Indicated by Degree of Denervation Fibrillation		
			L 4	L 5	S 1
Quadriceps femoris	L 2, L 3, L 4	Femoral	+++	(—)	(—)
Tibialis anterior	L 4, L 5, (S 1)	Peroneus profundus	++	++	(—)
Extensor hallucis longus	L 4, L 5, S 1	Peroneus profundus	+	++	+
Peroneus longus		Peroneus superficialis			
Gastrocnemius	L 5, S 1, S 2	Tibial	(—)	+++	++
Soleus	(L 5), S 1, S 2	Tibial	(—)	+	+++

from the gastrocnemius (fifth lumbar nerve root) and minimal abnormal responses from the soleus (fifth lumbar and first sacral nerve roots). In addition to the maximal abnormal responses from the gastrocnemius, further aid in localization at the fifth lumbar nerve root is given by the absence of abnormal responses in the quadriceps femoris (second, third and fourth lumbar nerve roots) and the presence of abnormal potentials in the tibialis anterior, which is not innervated by the first sacral nerve root. The gluteal muscles are always tested to rule out a partial peripheral lesion of the sciatic nerve, since they are not innervated by this nerve.

With use of tables 1 and 2 and figures 4 and 5, it is possible accurately to localize compressive lesions of the sixth, seventh and eighth cervical nerve roots and of the fifth lumbar and first sacral nerve roots.

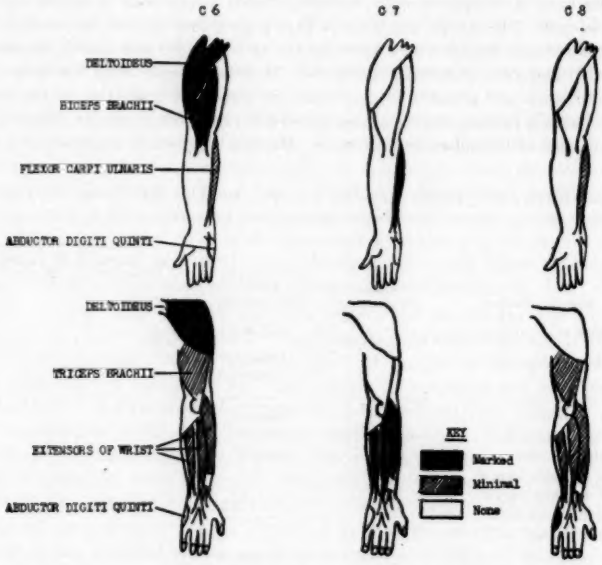

Fig. 4.—Degrees of denervation fibrillation following lesions of cervical nerve roots.

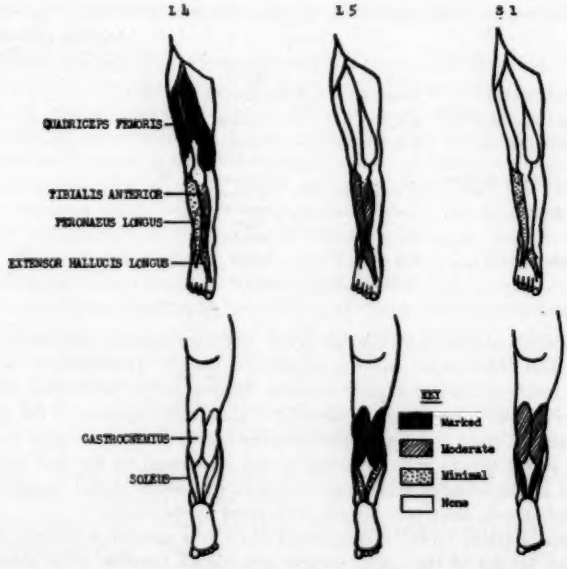

Fig. 5.—Degrees of denervation fibrillation in lesions of lumbosacral nerve roots.

Seventy-five patients were examined in this series, all of them at Mercy Hospital, San Diego. Fourteen had cervical lesions, 1 a thoracic lesion, and 60, lumbosacral lesions, as found at operation by two of us (W. W. W. and D. H. W.). Three of these lesions were tumors (an extradural metastatic carcinoma in the cervical region, an extradural neurofibroma of the upper thoracic region and an extradural metastatic carcinoma of the cauda equina). The remainder were compressive nerve root lesions produced by a frankly herniated nucleus pulposus, a protruded intervertebral disk or other extrinsic factors.

Electromyographic localization was made independently and without previous knowledge of the clinical or myelographic diagnosis. In other words, using the method of examination illustrated in tables 1 and 2 and figures 4 and 5, the electromyographer (P. A. S.) was completely uninfluenced by previous diagnostic procedures.

The results were checked against the myelograms taken after injection of ethyl iodophenylundecylate, in 68 of the 75 cases, and confirmed by operation (table 3).

TABLE 3.—*Comparison of Electromyographic, Myelographic and Operative Findings*

Root Lesion Found at Operation	Electromyogram		Myelogram	
	Correct	Incorrect	Correct	Incorrect
C 2 to C 5 (tumor)	1	0	0	1
C 6	1	0	1	0
C 7	8	1	6	1
C 8	2	0	1	1
No lesion	1	0	..	..
Total cervical lesions	13	1	8	3
Th 10 (tumor)	1	0	1	0
Total thoracic lesions	1	0	1	0
L 4 (tumor)	1	0	1	0
L 5	22	1	19	3
S 1	30	5	27	3
No lesion	1	0	2	1
Total lumbosacral lesions	54	6	48	7
Totals	68 (90.7%)	7 (9.3%)	58 (85.3%)	10 (14.7%)

RESULTS

Correct localization of the spinal nerve root or roots compressed was made by the electromyogram in all but 7 cases. In analyzing these 7 cases, we found that the electromyogram showed evidence of compression of the spinal nerve root in all instances. What, then, was the source of error in determining the exact nerve root involved? In 1 case (cervical herniated nucleus pulposus) the electromyographer placed the needle electrode incorrectly before operation. After operation a check electromyogram revealed the correct localization. In 3 cases no evidence of root compression could be seen in the preoperative ethyl

iodophenylundecylate myelogram, and nothing abnormal was encountered at the time of surgical exploration. These 3 patients, however, have been followed and have been found to have been definitely relieved of their sciatic pain. This would seem to indicate that root compression had actually existed (as shown by the electromyogram alone) and was relieved by a simple laminectomy with decompressions of the root. In the remaining 3 cases the electromyogram revealed involvement of the first sacral nerve root, whereas myelograms taken with ethyl iodophenylundecylate and operation both showed the compressive lesion to be at the fourth lumbar intervertebral space. On reviewing the myelographic and the operative observations, a fairly obvious reason for the false anatomic localization by the electromyogram was found. In

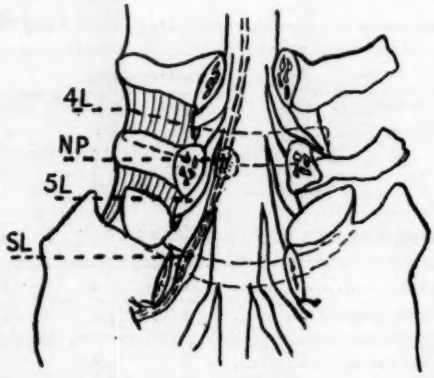

Fig. 6.—Diagram showing how a medially and inferiorly herniated nucleus (*N P*) pulposus at the fourth lumbar interspace may compress the first sacral nerve root (*S L*). *4 L* indicates the fourth lumbar intervertebral disk, and *5 L*, the fifth lumbar nerve root.

these cases the lesion was a herniated nucleus pulposus which had protruded medially and inferiorly at the fourth lumbar space not to involve the fifth nerve root but actually to impinge on the fibers of the first sacral nerve root intradurally (fig. 6). The electromyogram, then, was correct in localizing the involved nerve root, but the compression, instead of being at the lumbosacral space, where the first sacral nerve root emerges from the dura, was actually at the fourth lumbar interspace. Therefore, when the electromyogram shows the first sacral nerve root to be involved, the surgeon must keep in mind that the lesion may be situated either medially, at the fourth lumbar interspace, or laterally, at the lumbosacral space.

Myelographic studies with ethyl iodophenylundecylate were made in 68 of the 75 cases, and an incorrect diagnosis was made in 10. In 2

of these 10 cases, false localizations were made, and in the other 8 cases no localization could be made, usually because of a narrow spinal canal. Of these 10 cases, the electromyogram gave the correct localization in all but 1, as proved by operation. The usefulness of the electromyogram in cases in which myelographic evidence is absent is well illustrated by our case of metastatic carcinoma in the cervical region. The myelogram taken with ethyl iodophenylundecylate failed to reveal any evidence suggesting a compressive lesion of the nerve root; yet the electromyogram revealed denervation fibrillation of the muscles innervated by the second through the fifth cervical nerve roots. Operation confirmed

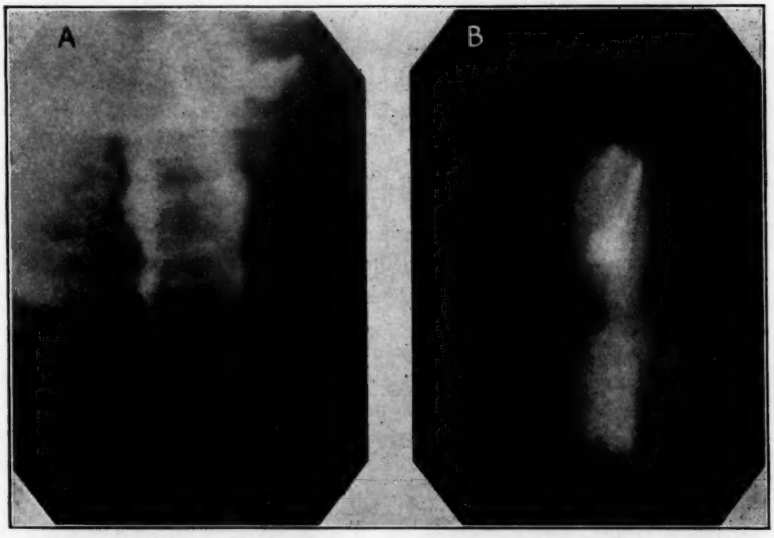

Fig. 7.—*A*, absence of changes in the myelogram of the cervical region of the spine in a case in which the electromyogram revealed the lesion at the second to the seventh cervical nerve root. An extradural metastatic carcinoma at the second to the fifth cervical nerve roots was found at operation.

B, false localization of a lesion in the space between the third and the fourth lumbar nerve root. The lesion was localized in the electromyogram at the fifth lumbar nerve root (between the fourth and the fifth lumbar nerve root). A herniated nucleus pulposus compressing the fifth lumbar nerve root was found at operation.

the electromyographic localization of the malignant extradural lesion. Figure 7 illustrates each of the two types of myelographic error.

SUMMARY

Electromyographic examinations, utilizing the monopolar needle electrode technic and a cathode ray oscilloscope, were made in 75 consecutive cases of compressive lesions of spinal nerve roots. Of these

lesions, 14 were cervical, 1 was thoracic and 60 were in the lumbosacral region. The majority of these lesions were due to derangements of the intervertebral disks. The diagnosis of the specific nerve root compressed was made by finding voltages characteristic of denervation fibrillation arising only from the skeletal muscles supplied by that particular nerve root. This electromyographic method was found to be accurate in localizing exact lesions of nerve roots in 68 of 75 cases in which it was used. The 7 cases of error in localization are discussed. Myelographic study with ethyl iodophenylundecylate was correct in localizing the spinal level of compression in 58 of the 68 cases in which it was done. The accuracy of both methods was evaluated by the operative findings.

CONCLUSIONS

1. Recent advances in electronics have made possible the clinical use of electromyography in the diagnosis of neurologic lesions.

2. In compressive lesions of nerve roots the electromyographic method has a high degree of accuracy in determining not only the presence of such a lesion but also its exact location.

3. Electromyography which utilizes needle electrodes placed intramuscularly in direct contact with the fibers and a cathode ray oscilloscope is more accurate than the method using percutaneous electrodes and an ink-writing recorder.

4. The use of electromyography in conjunction with clinical examinations and ethyl iodophenylundecylate myelography results in a more accurate and an earlier diagnosis in cases of the spinal nerve root compression syndrome.

General Review

CHEMISTRY OF WALLERIAN DEGENERATION

A Review of Recent Studies

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DEMYELINATION, or the destruction of the myelin sheath of nerve fibers, is a prominent characteristic of many neurologic disorders. An understanding of the chemical changes associated with demyelination is obviously desirable. A study of these changes is practicable only if there is available a ready means of producing the destruction of "myelin" experimentally. Technics for the production of an experimental demyelination in the central nervous system have been reviewed in papers by Putnam and his colleagues,[1] Hurst[2] and, more recently, Wolf, Kabat and Bezer.[3] More convenient for a chemical study, however, is the well known wallerian degeneration of the distal segment of a cut peripheral nerve. This type of degeneration can be easily produced in the laboratory and has the added advantage that the histologic changes are well understood and have often been described.[4]

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1. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. Putnam, T. J.: Studies in Multiple Sclerosis: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

2. Hurst, E. W.: Review of Some Recent Observations on Demyelination, Brain **67**:103, 1944.

3. Wolf, A.; Kabat, E. A., and Bezer, A. E.: Pathology of Acute Disseminated Encephalomyelitis Produced Experimentally in the Rhesus Monkey and Its Resemblance to Human Demyelinating Disease, J. Neuropath. & Exper. Neurol. **6**:333, 1947.

4. (*a*) Howell, W. H., and Huber, G. C.: Physiological, Histological and Clinical Study of the Degeneration and Regeneration in Peripheral Nerve Fibres After Severance of Their Connections with the Nerve Centres, J. Physiol. **13**:335, 1892. (*b*) Mönckeberg, G., and Bethe, A.: Die Degeneration der markhaltigen Nervenfasern der Wirbelthiere unter hauptsächlicher Berücksichtigung des Ver-

(Footnote continued on next page)

Rarely have the technics of chemistry been applied to degenerating nerves. Notable exceptions are the pioneer studies of Noll [5] and Mott and Halliburton [6] and, more recently, those of May and his associates,[7] Abercrombie and Johnson [8] and Brante.[9] The current ideas on the chemistry of demyelination have been reviewed by Gerard [10] and Page.[11] Many of them stem from the original work of Halliburton,[12] who stated the belief that the chief phosphorus-containing lipid of the nervous system was "protagon," which yielded lecithin and cerebrin on decomposition. It is now known that lecithin (i. e., phosphatidyl choline) is of minor importance in the structure of the myelin sheath of a mammalian nerve fiber and that the former belief that protagon was a pure chemical substance hindered the development of knowledge of the chemical nature of "myelin" for many years.

Another reason for ignorance of the chemistry of the myelin sheath is the inadequacy of some of the older technics for lipid analysis; large

haltens der Primitivfibrillen, Arch. f. mikr. Anat. **54**:135, 1899. (*c*) Ranson, S. W.: Degeneration and Regeneration of Nerve Fibers, J. Comp. Neurol. **22**:487, 1912. (*d*) Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vols. 1 and 2. (*e*) Spielmeyer, W.: Degeneration und Regeneration am peripherischen Nerven, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 9, p. 285. (*f*) Nageotte, J.: Sheaths of the Peripheral Nerves: Nerve Degeneration and Regeneration, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, p. 189. (*g*) Weddell, G., and Glees, P.: The Early Stages in the Degeneration of Cutaneous Nerve Fibers, J. Anat. **76**:65, 1941. (*h*) Young, J. Z.: The Functional Repair of Nervous Tissue, Physiol. Rev. **22**:318, 1942. (*i*) Weiss, P.: The Technology of Nerve Regeneration: A Review; Sutureless Tubulation and Related Methods of Nerve Repair, J. Neurosurg. **1**:400, 1944.

5. Noll, A.: Ueber die quantitativen Beziehungen des Protagons zum Nervenmark, Ztschr. f. physiol. Chem. **27**:370, 1899.

6. Mott, F. W., and Halliburton, W. D.: VIII. The Chemistry of Nerve-Degeneration, Philos. Tr. R. Soc., London, B **194**:437, 1901.

7. May, R. M.: Études microchimiques sur le système nerveux: III. L'eau et les combinaisons phosphorées du nerf au cours de sa dégénérescence, Bull. Soc. chim. biol. **12**:934, 1930. May, R. M., and Arnoux, J.: Études microchimiques sur le système nerveux: IV. Les combinaisons azotées du nerf au cours de sa dégénérescence, ibid. **22**:286, 1940.

8. Abercrombie, M., and Johnson, M. L.: Collagen Content of Rabbit Sciatic Nerve During Wallerian Degeneration, J. Neurol., Neurosurg. & Psychiat. **9**:113, 1946.

9. Brante, G.: Studies on Lipids in the Nervous System with Special Reference to Quantitative Chemical Determination and Topical Distribution, Acta physiol. Scandinav. (supp. 63) **18**:1, 1949.

10. Gerard, R. W.: Nerve Metabolism, Physiol. Rev. **12**:469, 1932.

11. Page, I. H.: Chemistry of the Brain, Springfield, Ill., Charles C Thomas, Publisher, 1937.

12. Halliburton, W. D.: The Chemical Side of Nervous Activity, Lancet **1**:1659, 1901.

samples of tissue were required, and usually only a single lipid could be measured at one time. Recently, however, micromethods have been developed that allow the simultaneous determination of a number of lipids in one small sample. In experiments reported by us [13] these methods have been applied to the small piece of tissue available from the degenerating segment of the sectioned sciatic nerve of the cat.

LIPIDS OF THE NERVOUS SYSTEM

The principal lipids of the nervous system are the following: (*a*) Neutral fat, i. e., esters of glycerin and fatty acids. (*b*) Cholesterol. The cholesterol of the nervous system is usually present as the free sterol, but, as will be seen later, esters of cholesterol appear during wallerian degeneration. (*c*) Cerebroside. Cerebroside, because it contains one unit of galactose per molecule, is sometimes called a glycolipin or a galactolipin. (*d*) Phospholipids. Each molecule of phospholipid contains one phosphoric acid group. The principal phospholipids are lecithin, cephalin and sphingomyelin. Folch [14] has recently shown that the cephalin of the central nervous system is a mixture of at least three phospholipids: phosphatidyl serine, phosphatidyl ethanolamine and brain diphosphoinositide. Lecithin (phosphatidyl choline) and two of the components of brain cephalin, phosphatidyl serine and phosphatidyl ethanolamine, are often called phosphoglycerides because, in addition to phosphoric acid, they also contain glycerin in their molecular structure. Similarly, sphingomyelin, which contains the base sphingosine, is called a phosphosphingoside. Since cerebroside also contains sphingosine, Carter and his associates [15] have grouped sphingomyelin and cerebroside together, under the general term sphingolipid.

The central nervous system contains much cholesterol, cerebroside and phospholipid, whereas in addition to these lipids, peripheral nerve also contains neutral fat, located chiefly in the connective tissue sheaths. Lipid represents some 20 per cent of the total fresh weight of the sciatic nerve of the cat and more than one-half the total solids of the nerve.

Myelin Sheath of a Mammalian Nerve Fiber.—Much of the lipid of peripheral nerve is in the myelin sheath. The lipid-containing sub-

13. Johnson, A. C.; McNabb, A. R., and Rossiter, R. J.: Chemical Studies of Peripheral Nerve During Wallerian Degeneration: I. Lipids, Biochem. J. **45**:500, 1949.

14. Folch, J.: Complete Fractionation of Brain Cephalin: Isolation from It of Phosphatidyl Serine, Phosphatidyl Ethanolamine, and Diphosphoinositide, J. Biol. Chem. **177**:497, 1949.

15. Carter, H. E.; Haines, W. J.; Ledyard, W. E., and Norris, W. P.: Biochemistry of the Sphingolipids: I. Preparation of Sphingolipids from Beef Brain and Spinal Cord, J. Biol. Chem. **169**:77, 1947.

stance of this sheath is frequently referred to as "myelin," the implication being that "myelin" is a definite chemical entity. "Myelin" has not been characterized chemically, and little is known either of its composition or of its structure. It is thought to be a complex of lipids and proteins, but the nature of this complex is far from perfectly understood.

Some idea of the lipids of the myelin sheath can be obtained by indirect means. The white matter of mammalian brain, which contains many myelinated nerve fibers, has a higher concentration of free cholesterol, cerebroside and sphingomyelin than has the gray matter, which contains most of the nerve cell bodies and comparatively few myelinated nerve fibers.[16] Peripheral nerve, which is also rich in "myelin," resembles the white matter of the brain rather than the gray matter.[17] This suggests that the principal lipids of the myelin sheath of a mammalian nerve fiber are free cholesterol, cerebroside and sphingomyelin.

The same conclusion is reached if the distribution of the lipids of the brain of an adult is compared with that of the lipids of the brain of a newborn infant. There is little difference in the distribution of the lipids of the gray matter, but the white matter of an adult brain, where myelination is complete, differs from the "white" matter of the brain of a newborn infant, where myelination is far from complete, in containing a higher concentration of the same three lipids, free cholesterol, cerebroside and sphingomyelin.[18]

Each of these lines of evidence indicates that the principal lipids of the myelin sheath are free cholesterol cerebroside and sphingomyelin. We have called these lipids the "myelin lipids," while Brante,[9] who made a similar study, referred to them as "sheath-typical." It in no way follows that these three substances are the only lipids contained in the myelin sheath. They are the lipids present in the greatest concentration and those that distinguish the myelin sheath from other parts of the nervous system. The myelin sheath may contain some lecithin, but our analyses show that considerable quantities of lecithin are also present in other, nonmyelin structures of the nervous system.

The position of cephalin is interesting. Since cephalin of the nervous system is a mixture of at least three individual lipids—phosphatidyl serine, phosphatidyl ethanolamine and brain diphosphoinositide—the exclusion of cephalin from the myelin lipids does not necessarily exclude any one of the individual constituents of cephalin. In fact, Brante[9]

16. Johnson, A. C.; McNabb, A. R., and Rossiter, R. J.: Lipids of Normal Brain, Biochem. J. **43**:573, 1948.

17. Johnson, A. C.; McNabb, A. R., and Rossiter, R. J.: Lipids of Peripheral Nerve, Biochem. J. **43**:578, 1948.

18. Johnson, A. C.; McNabb, A. R., and Rossiter, R. J.: Concentration of Lipids in the Brain of Infants and Adults, Biochem. J. **44**:494, 1949.

published data supporting the suggestion that phosphatidyl serine is a myelin lipid. Phosphatidyl ethanolamine has a distribution similar to that of lecithin and is not a myelin lipid, nor, according to Brante,[9] is brain diphosphoinositide. More data are required on these points.

From the foregoing discussion, it is seen that the principal myelin lipids are free cholesterol and the two lipids that contain the base sphingosine, cerebroside and sphingomyelin. Of the arrangement of these lipids in the myelin sheath and the nature of the lipoprotein complexes they form, little is known. The results obtained with the aid of the technics of polarization optics and roentgen ray diffraction, described by Schmitt and Bear,[19] and the recent roentgen ray diffraction studies of Elkes and Finean [20] are of great importance. It is possible, as Schmitt, Bear and Palmer [21] stated, that the sheath is "composed of concentrically wrapped layers of mixed lipides alternating with thin, possibly unimolecular layers of neurokeratinogenic protein material. Within the layers the lipide molecules are oriented with paraffin chains extending radially and with polar groups in the aqueous interfaces, loosely bound to those of protein."

LIPIDS DURING WALLERIAN DEGENERATION

Chart 1 shows the percentage change in the wet weight of a degenerating nerve. The water content of the nerve increases rapidly after section, reaching a maximum in four days. Thereafter the water content decreases steadily, and after eighty days there is no significant difference between the wet weight of a degenerating nerve and that of the intact controls. Chart 1 also shows that, whereas the total lipid decreases steadily throughout the course of degeneration, the myelin lipid (free cholesterol + cerebroside + sphingomyelin) decreases most rapidly during the period of eight to thirty-two days.

In chart 2 the data for total lipid and myelin lipid are given in terms of milligrams per hundred milligrams of fresh tissue, rather than as a percentage change. Chart 2 also shows the changes in the concentration of what is sometimes referred to as essential lipid, i. e., total cholesterol + total phospholipid + cerebroside. This decreases in a fashion similar to that of the myelin lipid. The neutral fat decreases rapidly at first, reaching a minimum between four and eight days after nerve section. The concentration of neutral fat then slowly increases, and by the end of thirty-two days it is the same as that of the control nerve.

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19. Schmitt, F. O., and Bear, R. S.: The Ultrastructure of the Nerve Axon Sheath, Biol. Rev. Cambridge Philos. Soc. **14**:27, 1939.

20. Elkes, J. J., and Finean, J. B.: Further Observations on the Structure of Frog Nerve Lipoprotein, J. Physiol. **108**:9 P, 1948.

21. Schmitt, F. O.; Bear, R. S., and Palmer, K. J.: X-Ray Diffraction Studies on the Structure of the Nerve Myelin Sheath, J. Cell. & Comp. Physiol. **18**:31, 1941.

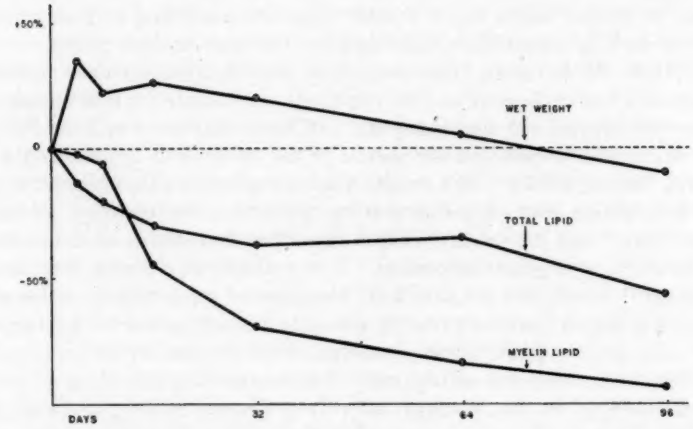

Chart 1.—Percentage change in the wet weight, total lipid and myelin lipid of cat peripheral nerve during wallerian degeneration.

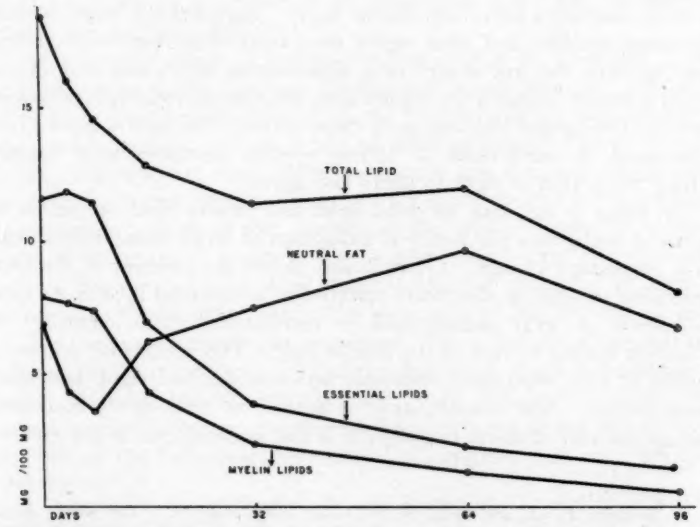

Chart 2.—Concentration of total lipid, neutral fat, essential lipid and myelin lipid of cat peripheral nerve during wallerian degeneration.

Chart 3 shows the interesting changes in the cholesterol content of the degenerating nerves. The concentration of total cholesterol changes little during the first eight days and then decreases steadily during the course of the degeneration. Free cholesterol, on the other hand, which accounts for almost all of the cholesterol of normal nerves, changes little during the first eight days and then decreases rapidly during the period of eight to thirty-two days, and thereafter more slowly. There is virtually no cholesterol ester in normal nerves, and during the period of the first eight days the concentration of cholesterol ester increases slowly. The cholesterol ester then increases rapidly, reaching a maximum at the end of sixteen days. After this time the cholesterol ester

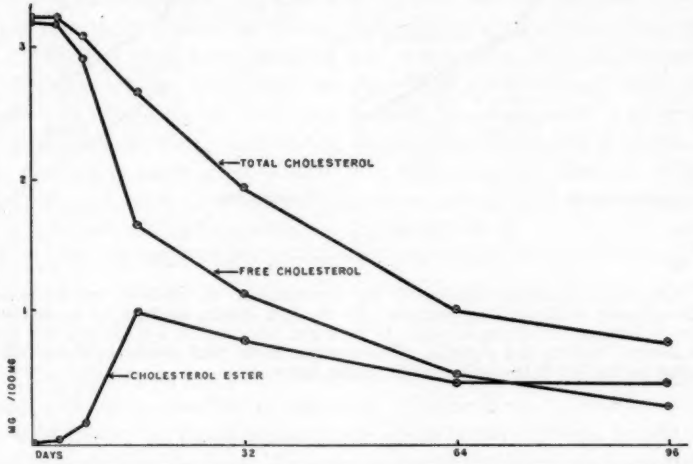

Chart 3.—Concentration of total cholesterol, free cholesterol and cholesterol ester of cat peripheral nerve during wallerian degeneration.

decreases, but more slowly than the free cholesterol, so that by ninety-six days more of the cholesterol is in the ester form than in the free form.

Of the individual phospholipids, sphingomyelin decreases at a rate similar to that of the total phospholipid; cephalin, more rapidly, and lecithin, more slowly. These findings are illustrated in chart 4. To the right, the change in each of the lipids of the nervous system, i. e., neutral fat, total cholesterol, lecithin and cephalin, is plotted as a percentage of the control value. None of these lipids disappears at a rate comparable with that of the total myelin lipid. To the left is plotted the percentage change for each of the individual myelin lipids, i. e., free cholesterol, sphingomyelin and cerebroside. Each of these lipids disappears at the same rate, suggesting further that these three substances exist together as the principal lipids of the myelin sheath.

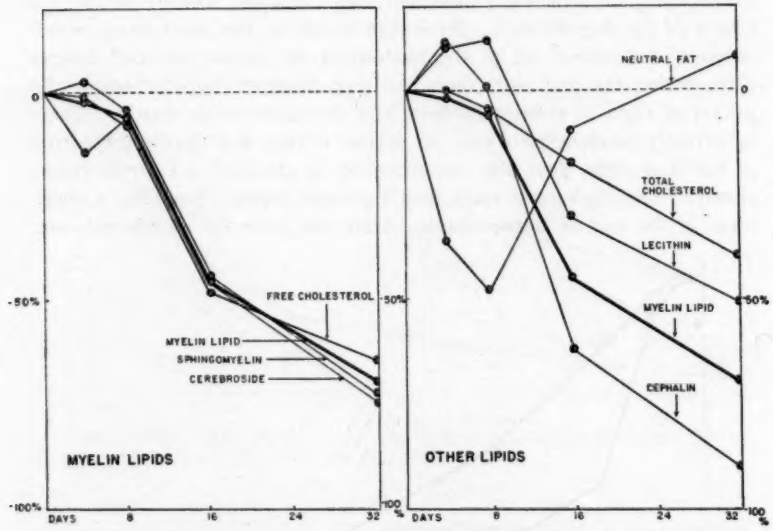

Chart 4.—Percentage change in the concentration of lipids of cat peripheral nerve during wallerian degeneration. To the left, myelin lipids, i. e., cerebroside, free cholesterol and sphingomyelin; to the right, other lipids, i. e., neutral fat, total cholesterol, lecithin and cephalin. The changes in the total myelin lipid are represented by the heavy line on each side of the figure.

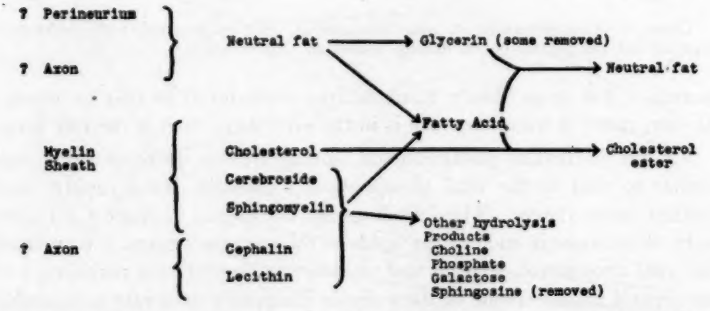

Chart 5.—Changes in lipids of cat peripheral nerve undergoing wallerian degeneration.

Chemistry of Demyelination.—In chart 5 are summarized some of the principal changes we have found in the lipids of cat peripheral nerve undergoing wallerian degeneration. It should be stressed that a chemical analysis is made of the whole nerve, and the figures represent not only the lipids of the myelin sheath but also those of the axon, Schwann cells, macrophages and perineurial and endoneurial connective tissue. The neutral fat is probably present chiefly in the perineurial connective tissue, but some may be in the axon. As degeneration proceeds, part of the neutral fat is quickly hydrolyzed into fatty acids and glycerin, some of which may be removed from the nerve. The sphingosine-containing lipids of the myelin sheath, i. e., cerebroside and sphingomyelin, together with cephalin and lecithin, are hydrolyzed into their constituent parts. Some of these hydrolysis products, e. g., choline, phosphate, galactose and sphingosine, may be removed, while some of the fatty acids, together with those formed from the hydrolysis of neutral fat, may combine with free cholesterol or glycerin to form cholesterol ester and neutral fat, respectively. Little is known of the location of cephalin or lecithin in a normal nerve. Because of the high concentration of these substances in gray matter, it is possible that they are normally present in the bodies of nerve cells and, presumably, in the axon of the peripheral nerve. As mentioned previously, cephalin is a mixture of lipids. It is possible that one or more of the individual constituents of cephalin may be found chiefly in the myelin sheath.

This represents our present concept of the chemical changes associated with demyelination of wallerian degeneration. Unfortunately, little is known of the changes in the lipids of the nervous system in the demyelinating diseases. In many instances pathologic demyelination is primary, i. e., independent of changes in the axon. In others it is secondary, i. e., the result of destruction of the axon. It is conceivable that the chemistry of pathlogic demyelination, especially secondary demyelination, is not greatly different from that of wallerian degeneration.

PARALLEL CHANGES IN STRUCTURE, FUNCTION AND CHEMISTRY OF A DEGENERATING PERIPHERAL NERVE

Degenerating peripheral nerve has been studied with the help of many experimental technics. The following account is an attempt to correlate in time the chemical changes in a degenerating nerve with other changes, both in structure and in function, that have been reported in the literature. It is convenient, for this purpose, to divide the degeneration that follows nerve section into three stages. Each fiber of a degenerating nerve does not degenerate at the same rate. The rate of degeneration is conditioned in part by the size of the fiber. There is

also a large variation in the rate of degeneration of different nerves in the same species and of similar nerves in different species. Since the observations to be mentioned in the following sections were frequently made on different nerves, often on different species, and often under different experimental conditions, the times assigned to each period must be regarded as approximations only. The degree of overlap between the stages, even for different fibers of the same nerve, is considerable.

STAGE 1.—*Period of Axon Destruction and Physical Destruction of "Myelin"* (no to eight days).—This stage is characterized by the physical disintegration of the myelin sheath, with little chemical destruction of the "myelin." It may be conveniently divided into an early stage (no to three days), during which the changes in the axon are slight and the nerve can still conduct an impulse, and a late stage (three to eight days), during which there is complete destruction of the axon and the ability of the nerve to conduct an impulse is lost.

Some of the changes in the early stage (no to three days) are seen within a few hours of nerve section. The axon at first swells, but very soon (ten hours) the swelling subsides and the diameter of the axon becomes less. The myelin sheath may lose some of its anisotropism, and the surface between the myelin sheath and the axon assumes a wavy outline. Many workers have confirmed the observation of Howell and Huber [18] that the nerve usually loses its ability to conduct an impulse on the third day after section. Heinbecker, Bishop and O'Leary,[22] in a study of the changes in the nerve action potential, found little change during the first twelve hours, but thereafter noted a progressive increase in the threshold of stimulus necessary to produce an impulse, an increase in the absolute refractory period and a reduction in the velocity of conduction. Rosenblueth and Dempsey [23] confirmed the progressive decrease in excitability and velocity of conduction and concluded that in any given fiber conduction fails more or less suddenly, at a time when excitability is still normal. Further evidence for this view is provided by the experiments of Erlanger and Schoepfle,[24] who failed to find any evidence for the contention of Rosenblueth and his collaborators [25] that the failure

22. Heinbecker, P.; Bishop, G. H., and O'Leary, J. L.: Nerve Degeneration in Poliomyelitis: III. Rate of Depression and Disappearance of Components of Conducted Action Potential in Severed Nerves; Correlation with Histologic Degeneration in Groups of Fibers Responsible for Various Components, Arch. Neurol. & Psychiat. **27**:1421 (June) 1932.

23. Rosenblueth, A., and Dempsey, E. W.: A Study of Wallerian Degeneration, Am. J. Physiol. **128**:19, 1939.

24. Erlanger, J., and Schoepfle, G. M.: A Study of Nerve Degeneration and Regeneration, Am. J. Physiol. **147**:550, 1946.

25. Rosenblueth and Dempsey.[23] Rosenblueth, A., and del Pozo, E. C.: The Centrifugal Course of Wallerian Degeneration, Am. J. Physiol. **139**:247, 1943.

of conduction progressed from the site of the injury toward the periphery. The electrical changes in degenerating frog nerve were studied by Parker [26] and Titeca.[27]

During the later stage (three to eight days) the axon disintegrates and finally collapses, while the myelin sheath fragments. Young [28] pictured the "myelin" as a viscous fluid compressed by the pressure of the axoplasm between the surface of the axon and the rigid tube formed by the neurilemma and the outer connective tissue sheath of Key and Retzius. The "myelin" wets the surface of the axon but not that of the tube wall. As the axon degenerates, the pressure exerted on the myelin sheath becomes less, and the "myelin," because of its surface tension, breaks up into segments, then into shorter and shorter ovoids and ultimately into spheres.

Chemically there is no great change in the concentration of the myelin lipids during the whole of stage 1. The "myelin" is probably still highly organized, for even when it is broken down into ovoids it retains some of its birefringence. Young,[4h] referring to the studies of Setterfield and Sutton,[29] with polarized light, stated that "the chemical break-up of the myelin involves its conversion to isotropic granules of triglycerides, which begins as early as the 18th hour and is complete by the 6th day." Setterfield and Sutton studied nerve degeneration in the rat. In our studies on the cat the chemical destruction of the myelin has barely started by the sixth day.

During this stage the wet weight of the nerve increases, probably owing to the uptake of water. There are also a decrease in the concentration of neutral fat and, according to May,[7] an increase in the concentration of protein phosphorus. This change, which may be associated with the axon, is being investigated further.

The degeneration of the axon is accompanied with a number of other interesting changes, which can be investigated only by specialized technics. The studies of De Robertis and Schmitt [30] with the electron

26. Parker, G. H.: The Progressive Degeneration of Frog Nerve, Am. J. Physiol. **106**:398, 1933.

27. Titeca, J.: Étude des modifications fonctionelles du nerf au cours de sa dégénérescence wallérienne, Arch. internat. de physiol. **41**:1, 1935.

28. Young, J. Z.: The History of the Shape of a Nerve-Fibre, in LeGros Clark, W. E., and Medawar, P. B.: Essays on Growth and Form Presented to D'Arcy Wentworth Thompson, New York, Oxford University Press, 1945, p. 41.

29. Setterfield, H. E., and Sutton, T. S.: The Use of Polarized Light in the Study of Myelin Degeneration, Anat. Rec. **61**:397, 1935.

30. De Robertis, E., and Schmitt, F. O.: The Effect of Nerve Degeneration on the Structure of Neurotubules, J. Cell. & Comp. Physiol. **32**:45, 1948.

microscope have shown that the neurotubules, fibrous structures within the substance of the axon, change very little during the first two days. Then, as the axon is destroyed, they shrink, fragment and finally disintegrate. Weddell and his collaborators [31] demonstrated that at this stage the axon is especially susceptible to staining with methylene blue administered intravenously. Abercrombie and Johnson [32] made a careful quantitative study of the changes in the nuclear population of a peripheral nerve during wallerian degeneration. There is no change in the total number of nuclei during the first two days, and then the nuclei begin to increase, and at such a rate that the increase in both tubal (chiefly Schwann cells) and endoneurial (macrophages and fibrocytes) nuclei relative to the number of cells already present is greatest during this period.

With the loss of the ability of the nerve to conduct an impulse, Sawyer [33] demonstrated a rapid decrease in the concentration of true cholinesterase, and Nachmansohn, John and Berman [34] claimed that the ability of the nerve to synthesize acetylcholine is lost. There is little change in the concentration of pseudocholinesterase, but von Muralt and his associates described a fall in the concentration of both acetylcholine [35] and thiamine.[36] Heinzen [37] reported an increase in the concentration of acid phosphatase activity. He stated the belief that this increase is related to the "chemical break-up of myelin." But, as has been pointed out, the available technics show that there is little chemical destruction of "myelin" during this period.

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31. Feindel, W. H.; Sinclair, D. C., and Weddell, G.: A New Method for Investigating the Nervous System, Brain **70**:495, 1947. Feindel, W. H., and Allison, A. C.: Intravenous Methylene Blue for Studying Fiber Degeneration in the Central Nervous System, Science **107**:429, 1948.

32. Abercrombie, M., and Johnson, M. L.: Quantitative Histology of Wallerian Degeneration: I. Nuclear Population in Rabbit Sciatic Nerve, J. Anat. **80**:37 (Jan.) 1946.

33. Sawyer, C. H.: Cholinesterases in Degenerating and Regenerating Peripheral Nerves, Am. J. Physiol. **146**:246, 1946.

34. Nachmansohn, D.; John, H. M., and Berman, M.: Studies on Choline Acetylase: II. The Formation of Acetylcholine in the Nerve Axon, J. Biol. Chem. **163**:475, 1946.

35. von Muralt, A., and von Schulthess, G.: Ueber den Acetylcholingehalt des peripheren Nerven während der Degeneration, Helvet. physiol et pharmacol. acta **2**:435, 1944.

36. von Muralt, A., and Wyss, F.: Ueber den Aneuringehalt des peripheren Nerven während der Degeneration, Helvet. physiol. et pharmacol. acta. **2**:445, 1944.

37. Heinzen, B.: Acid Phosphatase Activity in Transected Sciatic Nerves, Anat. Rec. **98**:193, 1947.

The over-all picture of stage 1 is essentially one of degeneration of the axon accompanied with loss of the ability of the nerve to react to natural and physiologic stimuli. There is a loss of enzymes that may be associated with the mechanism of the conduction of the nerve impulse, but there is little change in the chemistry of "myelin," although it may undergo physical disintegration and segmentation.

STAGE 2: *Period of Chemical Destruction of "Myelin"* (eight to thirty-two days).—This stage is characterized by the rapid disappearance of the "myelin." At the same time, the number of macrophages reaches a maximum, and the proliferation of the Schwann cells is at its height. Abercrombie and Johnson [32] showed that the macrophages and fibrocytes of the endoneurium increase in number about four times, while the nuclei of the Schwann cells increase by a factor of about 13. These figures are approximate and depend on the size of the nerve fiber studied.[38] During this time the wandering of the Schwann cells and fibroblasts of a degenerating nerve is also maximal.[39] The volume of the cytoplasm of the Schwann cells also increases, and the cells form the elongated Schwann bands, or bands of von Büngner. These eventually occupy the space left by the degenerating myelin sheath. During this stage there is also an increase in the concentration of acid phosphatase,[40] which may be correlated with the proliferation of the Schwann cells.

The water content of the degenerating nerve remains high, and there is a rapid decrease in the concentration of each of the myelin lipids. Cholesterol ester appears for the first time. Presumably, an enzyme system capable of destroying the myelin lipids now becomes active in the nerve. Another possibility is that the "myelin" is engulfed in particulate form by the macrophages and these cells remove themselves from the degenerating nerve to some other part of the body. The histologic evidence is that some of the "myelin" is engulfed by these cells, but it is probable that most of the enzymatic digestion takes place while the macrophage is in the nerve, rather than elsewhere. Otherwise it would be difficult to explain the increase in cholesterol ester.

The enzymes that destroy the cerebroside and phospholipids are not active in the normal tissue of the nervous system, for, despite many

38. Thomas, G. A.: Quantitative Histology of Wallerian Degeneration: II. Nuclear Population in Two Nerves of Different Fibre Spectrum, J. Anat. **82**:135, 1948.

39. Abercrombie, M., and Johnson, M. L.: The Outwandering of Cells in Tissue Cultures of Nerves Undergoing Wallerian Degeneration, J. Exper. Biol. **19**:266, 1942.

40. Heinzen.[37] Bodian, D.: Nucleic Acid in Nerve-Cell Regeneration, Symp. Soc. Exper. Biol., no. 1, p. 163, 1947.

claims to the contrary, there is no degradation of cerebroside and only slight change in phospholipid when brain or nerve is incubated in vitro. In addition, cholesterol is not esterified.[41] Some of the previously published claims may be attributable to bacterial contamination, for many micro-organisms are rich in lipid-splitting enzymes. It is possible that the great destruction of "myelin" that occurs in a degenerating nerve is brought about by an enzyme system derived from a type of cell which is absent, or present only in small numbers, in normal nerve, but which is present in great numbers at this stage of the degeneration. Two types of cell may be responsible. One, as has already been noted, is the macrophage; the other is the proliferating Schwann cell. Speidel[42] produced good evidence to support the view that the Schwann cell is responsible for the formation of "myelin." It is possible that the Schwann cells are also associated with its destruction. Evidence in favor of this view is the observation of Holmes and Young[43] that "myelin" first disappears from the outer surface of the sheath.

The suggestion that the Schwann cells provide the enzymes that destroy the myelin sheath is the converse of the suggestion of Abercrombie and Johnson[32] that the proliferation of the Schwann cells and endoneurial nuclei may be brought about by a chemical mediator released during the destruction of the nerve fiber. This chemical mediator is not likely to be one of the hydrolysis products of "myelin," since the specific growth rate of both Schwann cells and endoneurial nuclei is greatest in the period of three to eight days, a time when the chemical degeneration of the myelin sheath has scarcely begun. If a chemical mediator is responsible for the cellular proliferation, it seems more likely to be produced by the degenerating axon than by the degenerating myelin sheath. However, Joseph[44] has shown that twenty-one days after the section of the nonmyelinated anterior mesenteric nerve of the rabbit there is no increase in nuclei. This interesting observation could be interpreted as evidence favoring the view that when a myelinated nerve undergoes degeneration a chemical mediator is liberated from the myelin sheath. An alternative suggestion is that the cellular proliferation is brought about by physical factors. In a degenerating myelinated nerve the space left within the nerve sheath is much greater than that in a nonmyelinated nerve.

41. Johnson, A. C.; McNabb, A. R., and Rossiter, R. J.: Lipids of the Nervous System During in Vitro Degeneration, Canad. J. Research, Sect. E **27**:63, 1949.

42. Speidel, C. C.: Studies of Living Nerves: III. Phenomena of Nerve Irritation and Recovery, Degeneration and Repair, J. Comp. Neurol. **61**:1, 1935.

43. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, J. Anat. **77**:63, 1942.

44. Joseph, J.: Absence of Cell Multiplication During Degeneration of Non-Myelinated Nerves, J. Anat. **81**:135, 1947.

Another interesting chemical change reported by Abercrombie and Johnson [8] is the disappearance of the fraction of the protein nitrogen not readily extracted from the nerve with 0.1 normal sodium hydroxide. It is suggested that this residue of nitrogen may represent neurokeratin, a protein of the nervous system characterized by unusual properties of solubility. Neurokeratin may form part of the lipoprotein complex of the myelin sheath, and, in this respect, it is interesting to note that this nonextractable nitrogen disappears from a degenerating nerve at the same time as the myelin lipid.

It is also well known that the Marchi staining reaction can be obtained most readily during this stage, which Spielmeyer [4e] called the Marchi stage. The explanation usually offered for the susceptibility of degenerating "myelin" to the Marchi stain is that the phospholipid of the "myelin" is converted into neutral fat. This probably arises from the original statement of Mott and Halliburton [45] that "the chemical explanation of the Marchi reaction appears to be a replacement of phosphorised by non-phosphorised fat." It is now known that this explanation is not valid. However, we are no nearer to offering a satisfactory chemical explanation of the Marchi reaction.

It has long been known that if a nerve is incubated in vitro in isotonic sodium chloride solution many of the changes of stage 1 of the degeneration process can be seen. There are destruction of the axon and segmentation of the "myelin," but Feiss and Cramer,[46] Ingebrigtsen [47] and Abercrombie and Johnson [39] showed that under these conditions there is no proliferation of Schwann cells. Mönckeberg and Bethe [4b] stated that the same is true if a nerve is severed and allowed to remain in a recently killed animal. A nerve on incubation soon loses its ability to conduct an impulse. Boell [48] showed that the cholinesterase activity disappears, while De Robertis and Schmitt [30] demonstrated changes in the neurotubules characteristic of degeneration. There is, however, little change in the chemistry of the myelin lipid. It appears that if a nerve is incubated in vitro the degeneration is confined chiefly to stage 1 i. e., loss of function, loss of essential enzymes, destruction

45. Mott, F. W., and Halliburton, W. D.: The Chemistry of Nerve Degeneration, Lancet **1**:1077, 1901.

46. Feiss, H. O., and Cramer, W.: Contributions to the Histochemistry of Nerve: On the Nature of Wallerian Degeneration, Proc. Roy. Soc., London, s. B **86**:119, 1913.

47. Ingebrigtsen, R.: A Contribution to the Biology of Peripheral Nerves in Transplantation: II. Life of Peripheral Nerves of Mammals in Plasma, J. Exper. Med. **23**:251, 1916.

48. Boell, E. J.: Cholinesterase Activity of Peripheral Nerves, J. Cell & Comp. Physiol. **25**:75, 1945.

of the axon and fragmentation of the "myelin." Stage 2, the chemical destruction of "myelin" and the proliferation of nuclei of the Schwann cells and endoneurium, takes place only in vivo.

STAGE 3: *Thirty-Two Days On.*—In this, the final stage of the degeneration, the myelin sheath has almost disappeared and the Schwann cells, which by now have become Schwann bands, occupy the spaces left by the degenerated myelin sheath and axon. The number of cell nuclei of all types is considerably less. Both the endoneurium and the neurilemma become thickened and fibrous to form a tube, which shrinks down on the protoplasm of the Schwann cells. This tube is sometimes called the Schwann tube. Histologically, a great increase in the amount of endoneurial and perineurial collagen can be seen, an increase which Abercrombie and Johnson [8] demonstrated chemically. Chemical analyses also show that all the myelin lipid does not entirely disappear from the degenerating nerve. Glees [49] pointed out that myelin debris, stainable by the Marchi method, can be seen in a nerve eight months after section. Spielmeyer [46] referred to this final stage as the Scharlach red (scarlet red) stage, because at this time the nerve can be stained more readily with scarlet red than by the Marchi method.

Early in stage 3 the fiber is still capable of reinnervation. If a new axon does not grow into the prepared Schwann tube, the process of thickening and fibrosis continues, until eventually the Schwann tube can no longer receive a growing axon tip.

SUMMARY

Recent observations on the chemistry of the myelin sheath are reviewed. "Myelin" is not a characterized chemical entity. It consists of lipids and protein bound together in a highly organized complex. The principal lipids of this complex, i. e., the myelin lipids, are free cholesterol and two lipids that contain the base sphingosine—cerebroside and sphingomyelin. It is possible that some other lipid e. g., phosphatidyl serine, a component of cephalin, may also be a myelin lipid.

The process of wallerian degeneration may be divided into three stages: Stage 1 (no to eight days) is a period during which the axon is destroyed and the myelin sheath is fragmented, but not degraded chemically. It can be divided into an early stage (no to three days), during which there are only slight changes in the structure of the axon and the nerve retains its ability to conduct an impulse. This is followed by a later stage (three to eight days), during which there are complete disintegration of the axon, fragmentation of the myelin sheath, loss of ability of the nerve to conduct an impulse and loss in the activity of the

49. Glees, P.: The Marchi Reaction: Its Use on Frozen Sections and Its Time Limit, Brain **66**:229, 1943.

enzymes that possibly are associated with the transmission of the impulse. Stage 2 (eight to thirty-two days) is a period during which there is the greatest chemical destruction of "myelin." The myelin lipids disappear, and cholesterol ester is formed. There is a great increase in the number of macrophages and nuclei of the Schwann cells. Marchi staining is readily obtained. The degeneration of stage 1 can occur in vitro, but that of stage 2 can occur only in vivo. Stage 3 represents the final changes that take place after the "myelin" has disappeared. The endoneurium and neurilemma become thickened to form the Schwann tube, and the collagen content of the nerve greatly increases.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DEVELOPMENT OF THE MOTOR NUCLEI OF THE FACIAL NERVE IN MAN. ANTHONY A. PEARSON, J. Comp. Neurol. **85**:461 (Dec.) 1946.

Pearson studied the progressive grouping of the motor cells of the facial nucleus in older human embryos, fetuses and the adult human brain stem. The sections were stained with Bodian's method and with pyridine silver. Early in the third fetal month the outline of the nucleus begins to be fairly defined. In the fourth month there appears a small group of cells above the main mass. The small group is the beginning of the accessory nucleus, and the large mass is the chief motor nucleus of the facial nerve. During the fourth month the chief nucleus begins to be subdivided into groups of cells. First, it is divided into three columns of cells, which are approximately parallel with the long axis of the medulla. Additional cell groups begin to make their appearance in fetuses 4 and 5 months of age. In a full term fetus six subdivisions of the chief nucleus are usually seen, namely, dorsal, intermediate, ventral, medial, ventrolateral and ventromedian. All the nuclear groups appeared better defined in the older stages studied. The cells of the accessory nucleus probably supply striated muscle and are simply cells which have not migrated as far as the cells of the chief nucleus. The superior salivatory nucleus could not be identified. More work will be necessary in order to establish definitely the location of the cells of origin of the autonomic fibers of the facial nerve.

ADDISON, Philadelphia.

RETROGRADE DEGENERATION OF THE THALAMUS FOLLOWING PREFRONTAL LOBOTOMY. WALTER FREEMAN and JAMES W. WATTS, J. Comp. Neurol. **86**:65 (Feb.) 1947.

Freeman and Watts made anatomic studies on the brains of 12 adults on whom they had previously performed a prefrontal lobotomy for the relief of mental disorders. Four of the brains are described.

At operation the connections between the thalamus and the frontal pole had been severed in both hemispheres. The site of the coronal incisions was the level of the genu of the corpus callosum. In one case, two and a half years after the first operation a second incision had been made at a short distance behind the level of the genu. The illustrations show that practically all the white substance was cut but that the cortex for the most part was left intact. The time of survival of the patients varied from four months to two years. Sections of the thalamus were cut 20 microns thick. For comparison in each case, a normal brain was sectioned in the same plane as that in the operative procedure, and comparable sections from the normal and the lobotomized brains were stained for cells and myelin sheaths. The criteria used for identifying the areas of degeneration were loss of ganglion cells and proliferation of the oligodendroglia. The findings agree well with previous experimental observations in nonhuman primates. The cells whose axons run to cortical areas 9, 10, 11 and 12 are situated in the medial nucleus of the thalamus; those whose axons run to the medial surface of the hemisphere, in the anterior nucleus, and those whose axons go to

areas 4, 6 and 8, in the lateral group of nuclei. This study points to the importance of the medial nuclei of the thalamus as the anatomic substrate for emotional experiences.

ADDISON, Philadelphia.

RESULTS OF UNILATERAL AND BILATERAL EXTIRPATION OF THE FOREBRAIN OF AMBLYSTOMA. S. R. DETWILER, J. Exper. Zool. **100**:103 (Oct.) 1945.

Lurching, engulfing food, chewing and swallowing can be carried out in an integrated manner by Amblystoma larvae that lack cerebral hemispheres, eyes and nasal sacs. Such activities are less vigorous than those of larvae with intact hemispheres. The reduction of spontaneous foraging activity results in less food intake and great retardation of growth.

Larvae with intact hemispheres but lacking eyes and nasal organs can keep pace with the growth of normal control larvae under conditions of maximal feeding. Hence the lateral line sense organs alone constitute an adequate receptor apparatus for the detection of food in motion.

A comparative study of the sizes and volumes of the medullas of parabiotic twins in which one component had been deprived of the presumptive cerebral hemispheres (in stage 21) was made. The hemispheres do not appear to exert any morphogenic influence on the medulla.

There was no regeneration of the ipsilateral cerebral hemisphere when half the forebrain, including the optic and olfactory rudiments, was removed from embryos in stage 21. These results confirm the previous findings that the hemisphere will not regenerate in the absence of the nasal placode. In such animals the contralateral, remaining hemisphere underwent a marked compensatory increase in size, which was due to cellular hyperplasia. Although the ipsilateral nasal sac showed compensatory increase in size, this was not sufficient to account for the greater developmental response in the hemisphere.

Striking deformities in the morphology of the head, with pronounced reduction of the upper jaw, resulted from excision of the forebrain. The lower jaw was unaffected.

REID, New Brunswick, N. J.

THE NERVOUS SYSTEM AND REGENERATION OF THE FORELIMB OF ADULT TRITURUS: VII. RELATION BETWEEN NUMBER OF NERVE FIBERS AND SURFACE AREA OF AMPUTATION. MARCUS SINGER, J. Exper. Zool. **104**:251 (March) 1947.

When the quantity of nerve fibers required for regeneration of the forelimb of the newt Triturus viridescens is expressed in terms of the number of nerve fibers per unit area of amputation surface (either the total area or the area of the soft tissues only), the requirements for regeneration are found to be a constant in such widely separated regions as the digits and the upper arm. The fiber requirements of each level of the limb depend on the quantity of tissue present at the amputation surface rather than on the extent of the injury, the size of the stump, other limb levels or the number of nerve fibers available at the latter or at another region of the limb.

The hand is the exception to the rule of the constant number of fibers per unit area, since it requires less than half the quantity of nerve fibers per unit area that are needed elsewhere. Therefore, the hand appears to be more sensitive to the influence of the nerves than other regenerating parts of the limb. The factors which might account for the kind of regeneration found in the hand are presented in the discussion, which also summarizes the influence of nerve on regeneration.

REID, New Brunswick, N. J.

Physiology and Biochemistry

VOLUNTARY DISSOCIATION OF THE ACCOMMODATION AND THE CONVERGENCE FACULTY. C. KIETH BARNES, Arch. Opth. **41**:599 (May) 1949.

The relation which exists between accommodation and convergence is definite and significant. Many persons have volitional control of convergence; at the command, "Cross your eyes," they are able to do so with ease. Others cannot, but after a period of tutelage they acquire the faculty. This faculty seems to be the result of conditioning at a subconscious level, since the position of convergence can be held in the presence of distracting influences and the diversion of conscious thought.

These voluntarily induced periods of convergence are usually accompanied with corresponding increases in accommodation. A very common demonstration of this is the ease with which one can achieve stereopsis without a stereoscope by developing a voluntary control of accommodation and convergence.

The author reports two interesting sets of observations on, as he describes them, "ocular gymnastics." The first of the two was made on himself; the second during the examination of an interesting patient.

The first observations suggested that the psychic concept of the location of the horopter in space is primarily related to convergence rather than to accommodation. It also suggested that the psychic magnification of near objects, and minification of distant objects in excess of that based on the law of the square of the distance, is predicated on convergence primarily rather than on accommodation.

The second observation involved an unusual case of fusion anomaly in which lifelong functional parallelism appeared to depend on alternation at or above the frequency of a flicker. It is believed that this case may be evidence in favor of the theory of physiologic alternation as a basis of fusion.

SPAETH, Philadelphia.

ON THE REQUIREMENT FOR DIPHOSPHOPYRIDINE NUCLEOTIDE IN THE AEROBIC METABOLISM OF PYRUVATE BY BRAIN TISSUE. J. LARNER, B. J. JANDORF and W. H. SUMMERSON, J. Biol. Chem. **178**:373, 1949.

There appears to be general agreement that at least the following cofactors are necessary for the restoration of normal aerobic utilization of pyruvate in brain suspensions after dialysis: (*a*) inorganic phosphate, (*b*) magnesium ions, (*c*) adenylic acid or adenosine triphosphate and (*d*) a C_4-dicarboxylic acid. The participation of diphosphopyridine nucleotide as an additional cofactor, however, has not as yet been unequivocally demonstrated. Diphosphopyridine nucleotide was, however, found by Larner, Jandorf and Summerson to be an essential cofactor in the oxidation of pyruvic acid by water-homogenized mouse brain preparations. Other cofactors required for the demonstration of aerobic metabolism of pyruvate with such preparations include inorganic phosphate, Mg^{++}, adenosine triphosphate, fumarate and cytochrome c. The requirement for the addition of diphosphopyridine nucleotide to homogenized brain preparations for the promotion of pyruvate oxidation becomes apparent only when the tissue is highly homogenized. Coarse homogenates do not require added diphosphopyridine nucleotide in pyruvate oxidation. It is not necessary to add the substance to highly homogenized preparations if homogenization is conducted in 1 to 3 per cent nicotinamide solutions instead of in water alone. Evidence is presented that the liberation or activation of the intracellular enzyme of diphosphopyridine nucleotidase is of importance in the demonstration of the role of the substance in pyruvate oxidation by brain homo-

genates. Highly homogenized brain preparations have a more pronounced diphosphopyridine nucleotidase activity than coarse homogenates, and nicotinamide presumably inhibits such enhanced activity. Conflicting results of previous workers on the requirement for diphosphopyridine nucleotide in pyruvate metabolism by brain tissue may have been due to variations in the mode of tissue preparation.

PAGE, Cleveland.

ON THE MECHANISM AND LOCALIZATION OF THE SYMPTOMS OF ELECTROSHOCK AND ELECTRONARCOSIS. A. VAN HARREVELD, J. Neuropath. & Exper. Neurol. **6**:177 (April) 1947.

The effects of electric shock and electric narcosis have generally been studied in animals with an intact central nervous system. In the present study, three categories of experiments were performed on decerebrate dogs in which, by a section through the midbrain, the influence of the hemispheres, the diencephalon and part of the mesencephalon was eliminated. Experiments were performed on 5 dogs in which one hindlimb was deafferented. Such preparations allowed conclusions regarding the reflex nature of some of the symptoms observed. In some instances this procedure was combined with decerebration. Finally, the experiments were performed on 5 dogs which were subjected to unilateral decortication and on 2 animals which were subjected to bilateral decortication. The effects of electric shock and electric narcosis on these animals were compared with the syndrome of shock and narcosis in dogs which were not subjected to any of the aforementioned surgical procedures.

It was observed that in the decerebrate preparations shock and narcosis produced an enhancement of the decerebrate rigidity and an increase in the respiratory rate. It was postulated that in the normal animal these symptoms of medullary stimulation are masked by inhibition, produced by the stimulation of structures situated rostral to the decerebration section in the midbrain.

The respiratory arrest observed in the course of electric shock and electric narcosis in the intact animal was considerably shortened in the decerebrate preparation. This indicates that the arrest in the normal animal is not caused by a paralyzing action of the current directly on the respiratory center, but, again, by inhibition of that center.

Unilateral and bilateral decortication did not produce major changes in the symptoms of electric shock and electric narcosis. This may indicate the relative unimportance of the cortex for the production of these syndromes.

The observations on animals with one deafferented limb made it clear that in general no spinal reflex mechanism is involved in the production of the extensor contractions which are part of the symptoms of shock and narcosis.

GUTTMAN, Wilkes-Barre, Pa.

DIET OF MOTHER AND BRAIN HEMORRHAGES IN INFANT RATS. E. E. BROWN, J. E. FUDGE and L. R. RICHARDSON, J. Nutrition **34**:141 (Aug.) 1947.

Brown and his co-workers reared female rats to maturity on a synthetic diet that was deficient in vitamin K. If lard was removed from their diet and the females were allowed to bear litters, a high incidence of cerebral hemorrhages ocurred in the offspring. The hemorrhages did not occur when the diet contained either lard or vitamin K. The blood coagulation time of females which produced hemorrhagic young and of young with visible hemorrhages was normal. This showed that the prothrombin level was not abnormally low. It is suggested that some substance which acts normally to maintain capillary strength is not

synthesized by the body when the diet is low in fat and deficient in vitamin K. An assay with chicks shows that lard may contain a small, but significant, amount of vitamin K.

J. A. M. A.

EXPERIMENTAL CONVULSIONS AND THEIR MODIFYING FACTORS: IV. ELECTROLYTES (POTASSIUM). J. ALVAREZ, S. ARROYO and S. OBRADOR, Bol. Inst. de estud. med. y biol. **3**:7 (Jan.-Feb.) 1945.

Convulsions were produced in experimental animals which were given potassium chloride by tube (0.10 to 0.5 Gm. per kilogram of body weight). An attempt was made to induce convulsions after two hours. To other animals divided doses of potassium chloride (up to 1.25 Gm. per kilogram) were given in the same manner over a period of sixty hours. No significant alterations in the convulsive threshold were noted in animals given potassium. In a few cases the convulsive responses were less intense. The authors conclude that potassium does not have a definite effect on the convulsive threshold. The reported retention of potassium during interparoxysmal periods and its elimination before and during an attack are secondary to the effect of the paroxysms on nervous activity and have nothing to do with the relation of potassium to the convulsive threshold.

N. SAVITSKY, New York.

Meningitis and Blood Vessels

SEQUELAE OF EPIDEMIC PAROTITIS WITH MENINGOENCEPHALITIS. VERA OLDFELT, Nord. med. **40**:2189 (Nov. 26) 1948.

Of 75 patents (25 children and 50 adults) with mumps and meningoencephalitis, 15 (3 children, 12 adults) were found on a follow-up examination three to five years later to have permanent after-effects. One child had total unilateral deafness; another, severe epilepsy, and an adult, vestibular dizziness. In the other patients, the sequels, though milder, gave constant annoyance. There were various ocular and aural symptoms; some patients presented symptoms of neurasthenic and endogenous obesity. There were also 5 doubtful cases. Oldfelt said that the late prognosis seems to be less favorable in the patients with distinct symptoms of encephalitis in the acute stage. No relation was seen between the cell count of the cerebrospinal fluid in the acute stage and the frequency of after-effects.

J. A. M. A.

Diseases of the Brain

CUSHING'S SYNDROME DUE TO TUMOR OF ADRENAL CORTEX: REPORT OF A CASE OF AN ELEVEN MONTH OLD INFANT, WITH APPARENT OPERATIVE CURE. HAROLD M. GOLDSTEIN, Am. J. Dis. Child. **78**:260 (Aug.) 1949.

Any brief summary would fail to do justice to this report; but of the conclusions reached by the author, the following may be mentioned:

1. Cushing's syndrome is differentiated from the adrenogenital syndrome by variable symptoms, clinical course, prognosis and therapy. The two conditions may be associated, or the former may exist in almost pure form with slight virilization, characterized by rapidly progressive obesity, chiefly involving the face, neck and trunk; osteoporosis; purplish striae of the skin; polycythemia; acne; cyanosis and purpura; alterations in carbohydrate metabolism; hypertension; and, occasionally, severe asthenia, polyuria, polydipsia and polyphagia. Differen-

tiation concerns adiposogenital dystrophy, the Laurence-Moon-Biedl syndrome, pineal tumors and tumors of the interpeduncular region at the floor of the third ventricle.

2. Statistics indicate that cases of Cushing's syndrome in which a pituitary adenoma was present were predominantly of persons over 10 years of age; cases in which the condition was due to benign or malignant tumors of the adrenal cortex were predominantly in children before puberty.

3. Excessive excretion of 17-ketosteriods may be expected in the urine of patients with Cushing's syndrome due to pathologic changes in the adrenal gland, and normal values will usually be obtained in cases in which there is no overt pathologic lesion.

4. Sectional roentgenography and perirenal insufflation are helpful aids in accurate lateralization of the tumor.

5. Early operation in cases of Cushing's syndrome is recommended to forestall death from tumor metastases, acute cerebrovascular and cardiovascular accidents, intercurrent infection, and inanition.

6. Hormone therapy must be instituted to support the patient until any remaining adrenocortical tissue may resume adequate function to support life. Fluids and electrolytes are extremely important.

7. Despite the development of improved diagnostic methods, operative technics, and hormonal preparations, the prognosis of this disease is poor.

JOHNS, Philadelphia.

THE BLINDSPOT SYNDROME. KENNETH C. SWAN, Arch. Ophth. **40**:371 (Oct.) 1948.

Swan discusses a situation in which the physiologic blindspot of a deviating eye in convergent strabismus is utilized by the patient to overcome the possible diplopia theoretically present whenever grossly disparate retinal areas receive similar stimuli. Diplopia in the peripheral fields may play an important role in the mechanism of binocular vision, but the normal person is little aware of peripheral double images when the eye is mechanically displaced. He may alternately fix with either eye, but his attention is on diplopia of the "object or area of regard."

One hundred and two cases were found to have in common certain symptoms and signs which have been designated as the blindspot syndrome.

The syndrome can be described, not as a fully established clinical entity, but, rather, as a means of calling the attention of ophthalmologists to cases of concomitant esotropia in which the physiologic blindspot of the squinting eye seems to play a special role in the alleviation of diplopia. It is hoped that the study of patients with this disorder in varying circumstances, with different technics by other ophthalmologists, will determine more fully the clinical significance of this mechanism.

Swan defines the syndrome as one of periodic diplopia, concomitant esotropia of 10 to 20 degrees, physiologic blindspot of the deviating eye overlying the area of regard, hypermetropia or anisometropia, normal retinal correspondence and potentialities for single binocular vision.

SPAETH, Philadelphia.

RISK OF NEUROLOGIC COMPLICATIONS IN PERNICIOUS ANAEMIA TREATED WITH FOLIC ACID. M. C. G. ISRAËLS and J. F. WILKINSON, Brit. M. J. **2**:1072 (Nov. 12) 1949.

Israëls and Wilkinson review observations on a group of 20 patients with pernicious anemia, who either had not been treated before or had relapsed, and whom

they treated with folic acid (pterolyglutamic acid) alone. Three had initial signs of subacute combined degeneration of the spinal cord. In a three year period, 13 patients without initial neurologic involvement showed signs and symptoms of subacute combined degeneration of the spinal cord, which were relieved by change of medication to liver extract or desiccated stomach preparations. Three patients with initial neurologic symptoms and signs became worse neurologically after folic acid therapy. Neither increasing anemia nor the hemoglobin levels could be used to predict the likelihood of neurologic complications. Four patients were well after two or three years of oral administration of 5 to 20 mg. of folic acid daily. The use of folic acid for the treatment of pernicious anemia should be strictly limited to cases of special difficulty. It should never be given patients with subacute combined degeneration of the spinal cord.

J. A. M. A.

Semeiologic Importance of Electroencephalography in Diagnosis of Epileptic Attacks in Children. L. Cornil, A. Cremieux and H. Gastaut, Semaine de hôp. de Paris **24**:1609 (July 2) 1948.

Cornil and his co-workers made electroencephalograms for 184 children between the ages of 6 and 13 years, 138 of whom had clinical epilepsy, while for 46 the diagnosis of epilepsy was doubtful from the clinical point of view. A typically normal tracing, taking into account the age of the child, furnishes presumptive evidence against the diagnosis of epilepsy, but does not provide definite proof. Positive diagnosis is made in the presence of two conditions: 1. When during rest one observes paroxysmal waves characterized by considerable amplitude, by their rhythmicity and sometimes by their regularity. Jasper's term of "hypersynchronic rhythm" seems to be appropriate, because these rhythms are very likely due to an excessive synchronization of the cortical neurons. 2. When one observes a slow dysrhythmia, which is incompatible with the age of the patient, in a child with nervous attacks of a definite, or nearly definite, epileptic nature. Electroencephalographic confirmation of the diagnosis of epilepsy was obtained for 90 per cent of the patients for whom a clinical diagnosis of epilepsy was made. The probability of epilepsy is suggested whenever a definitely pathologic tracing has been obtained which is not specific for epilepsy from a child presenting nervous attacks the epileptic nature of which has not been established clinically. Such pathologic tracings are represented in general by a slow dysrhythmia incompatible with the age, or by continuous or paroxysmal slow hypersynchronous waves which may be elicited by hyperpnea in a child with considerable hyperglycemia. The possibility of an epileptic process should be considered when one observes a pathologic, nonspecific tracing in a child presenting nervous attacks the epileptic nature of which appears unlikely from the clinical point of view.

J. A. M. A.

Prevention of Headache Following Spinal Anesthesia. J. P. Caccia, Prensa med. argent. **35**:2511 (Dec. 31) 1948.

Caccia prevented headache after spinal anesthesia by administering vitamin B intraspinally. He mixed 2.2 cc. of thiamine hydrochloride in sodium chloride solution, which contained 100 mg. of the vitamin, with the anesthesic solution to be injected intraspinally. The anesthetic effect was superior both in intensity and in duration. Headache was prevented. The author obtained favorable results from this method in more than 100 cases.

J. A. M. A.

ABSCESS OF THE LUNG AND OF THE BRAIN. M. JOSELEVICZ and M. KLEIMANS, Prensa méd. argent. **36**:63 (Jan. 14) 1949.

A man aged 34 presented symptoms of bronchopulmonary disease, cough and fever, which were controlled by penicillin. The roentgenologic examination of the thorax showed a cavity in the left lung. Examination of the sputum for tubercle bacilli gave negative results. Two months later the patient reentered the hospital complaining of loss of weight, aggravation of the bronchopulmonary symptoms, general cutaneous hyperesthesia and, for the preceding four days, constant acute headache and left hemiparesis. The cerebrospinal fluid was normal. Within four days meningitis developed, and the patient died in coma. An isolated, small abscess of the upper lobe of the left lung and an isolated abscess of the right cerebral hemisphere were found at necropsy. The case is unusual because of the development of only one cerebral abscess complicating the pulmonary abscess and also because of the seat of the abscess.

J. A. M. A.

Diseases of the Spinal Cord

MEDULLARY SYNDROMES SIMULATING MULTIPLE SCLEROSIS, AMYOTROPHIC LATERAL SCLEROSIS, SUBACUTE COMBINED DEGENERATION OF THE CORD AND SYRINGOMYELIA, CAUSED BY HERNIATION OF INTERVERTEBRAL CERVICAL DISK. W. A. DEN HARTOG JAGER and D. MOFFIE, Folia neurol. et neurochir. **2**:137 (April) 1949.

The authors report 9 cases in which the symptoms strongly resembled those of multiple sclerosis. The complaints were paresthesias of the hands and fingers and weakness and stiffness of the arms and legs. Brown-Séquard syndrome was present in 3 cases and in others the picture of lateral sclerosis. The roentgenograms in 5 of the 9 cases were normal; the Queckenstedt test showed a complete block in 2 cases, a partial block in 3 cases and a normal condition in 3 cases. In 7 cases the iodized oil (lipiodol®) test showed a block at the level of the fifth and sixth cervical segments. Herniation of a cervical disk differs from multiple sclerosis in the absence of remissions, psychic disturbances and involvement of cranial nerves and cerebellum. In only 2 cases was there a history of trauma. The protein of the spinal fluid was moderately elevated in 8 of 9 cases.

SJAARDEMA, Los Angeles.

Cranial and Peripheral Nerves

MALIGNANT RETROBULBAR NEURITIS. ADALBERT FUCHS, Arch. Ophth. **41**:60 (Jan.) 1949.

Fuchs opens his presentation with a statement which is quoted verbatim because of its interest: "In China one often sees cases which are difficult to explain."

This case report is one of severe acute bilateral retrobulbar neuritis which progressed to complete blindness in forty-eight hours. Complete atrophy of both optic nerves followed. Fuchs said that this was a special type of retrobulbar neuritis which he called malignant retrobulbar neuritis.

Three other cases are reported. Of the 4 cases, 3 had been seen within the past few months. Fuchs states that malignant retrobulbar neuritis is not rare in China.

SPAETH, Philadelphia.

PHARYNGEAL NEURILEMMOMAS OF CRANIAL NERVE ORIGIN: MEDICAL DISPLACEMENT OF THE INTERNAL CAROTID ARTERY AS A DIAGNOSTIC SIGN. D. SLAUGHTER and F. DE PEYSTER, Arch. Surg. **59**:386 Sept. 1949.

Pharyngeal neurilemmoma is a slowly growing, benign, encapsulated neoplasm with the histologic structure of a neurinoma. The tumors arise from the lower cranial nerves (tenth, eleventh and twelfth), the cervical nerves or the sympathetic trunk. Clinically the tumor is characterized by a submucosal firm, smooth mass protruding into the posterolateral pharyngeal area. There may be strong arterial pulsation at the medial circumference of the mass, caused by a displaced internal carotid artery. Paresis of the tenth, eleventh and twelfth nerves and/or of the cervical portion of the sympathetic trunk is frequently present. By means of aspiration biopsy, the tumor can be differentiated from mixed salivary tumor, lymphosarcoma, "lymphoepithelioma" of the tonsil, adenocarcinoma of the pharynx and tumor of the carotid body. The treatment is surgical removal. The lateral cervical approach is preferable to the transoral route because it permits clear exposure, retraction and dissection of the large blood vessels and avoids a potentially infected field.

LIST, Grand Rapids, Mich.

Diseases of the Blood Vessels

COSTOCLAVICULAR COMPRESSION: RELATION TO THE SCALENUS ANTICUS AND CERVICAL RIB SYNDROME. J. MCGOWAN and M. VELINSKY, Arch. Surg. **59**:62 (July) 1949.

Many symptoms attributed to the scalenus anterior (anticus) muscle are actually due to costoclavicular compression. The neurovascular structures passing to the arm are intermittently compressed, as in a vise, the jaws of which consist of the clavicle and cervical or first thoracic rib. The compression is readily produced by placing the shoulder in "attention position," resulting in reduction or obliteration of the brachial pulse. When some patients are tested for the scalenus syndrome by means of the Adson maneuver, they tend to push the shoulder down and back, thus causing obliteration of the pulse by costoclavicular compression. In such cases an erroneous diagnosis of scalenus syndrome may be made. A positive Adson sign, therefore, is diagnostically valid only when the patient is tested with his shoulders in relaxed and forward postion. The sign of costoclavicular compression and the Adson scalenus sign may occur in combination. The authors studied 25 Army recruits with neurovascular syndrome of the upper extremity. All 14 patients who had a positive costoclavicular syndrome showed the typical obliteration or reduction of the radial pulse on the affected side when assuming the "attention position." Of 108 supposedly normal controls, 4 showed a positive "attention" test, 3 of whom were later on proved to have a costoclavicular syndrome. Some patients were benefited by exercises strengthening the trapezius and levator scapulae. Scalenotomy may help because section of the scalenus muscle enlarges the costoclavicular space. Sometimes additional removal of a cervical rib, or even the first thoracic rib, may become necessary. Finally, the authors suggest that in intractable cases excision of the middle third of the clavicle may afford relief, although this procedure had not been tried in their material.

LIST, Grand Rapids, Mich.

Vegetative and Endocrine Systems

VARIOUS ASPECTS OF ATROPHY OF THE PITUITARY BODY. M. HERLANT, Acta clin. belg. **1**:197 (May-June) 1946.

Herlant made a pathologic and clinical study of Simmonds' disease in 3 women between the ages of 36 and 66 and a man aged 50 who were admitted to the St. Pierre Hospital in Brussels. The characteristic lesion associated with this disease is the destruction of the anterior lobe of the pituitary, caused by a specific or nonspecific inflammation or by a solid or cystic tumor. The author agrees with Sheehan that in women the atrophy of the pituitary is usually caused by postpartum thrombotic necrosis, although this was not true in the cases presented. The destruction of the anterior lobe of the pituitary is followed by secondary hypoplasia of the gonads, the thyroid and the adrenal cortex, similar to the atrophy observed in animals after hypophysectomy. The clinical symptomatology varies considerably, in contrast to the pathologic identity of the lesions of the endocrine organs. Cachexia was absent in all 4 patients, but all of them presented a dry, squamous skin and loss of axillary and pubic hair. In only 1 was myxedema simulated by manifestations of thyroid insufficiency.

J. A. M. A.

Treatment, Neurosurgery

USE OF TETANIZING CURRENT IN MYASTHENIA GRAVIS: REPORT OF CASE. J. L. RUDD and J. F. CULLINAN, Arch. Phys. Med. **29**:354 (June) 1948.

Rudd and Cullinan believe that involved muscles in a patient with myasthenia gravis could be kept in normal tone if exercised judiciously. They report the case of a man aged 53 who had ptosis of the right eyelid and who was supporting his mandible because of weakness of the masseter muscle. An attempt was made to increase the strength of the muscles and prevent progressive atrophy of disuse. The masseters were selected for treatment with a tetanizing current. Test results were used as a guide to determine the number of contractions to be eliminated during treatment. Improvement was noted within a week. In the fatigue tests, a greater number of contractions were produced without reaching the absolute fatigue point. After the patient had received the second treatment, ten contractions were elicited from the left masseter muscle; five days later in a fatigue test the number was 120. The number of contractions produced at treatment sessions between the aforementioned dates was seven. Two weeks later a fatigue test showed that the originally weaker right masseter had caught up with the left one, with 200 contractions elicited. After this test, sixty treatment contractions were given to each masseter. The patient lost the numbness on the right side of the face which had been present since the onset of the disease. Drooling from the side of the mouth, a source of considerable annoyance to the patient, had ceased. On palpation the masseters appeared to be of normal tone. The patient stated, "My face seems to be alive again." The final fatigue test was carried out on the forty-seventh day. Four hundred contractions were elicited from each masseter, an increase of approximately 400 per cent in forty-seven days. It was felt that the objective of increasing the strength of the masseter muscles had been reached.

J. A. M. A.

PHENURONE IN EPILEPSY. F. A. GIBBS, G. M. EVERETT and R. K. RICHARDS, Dis. Ner. System **10**:47 (Feb.) 1949.

Phenurone (phenacetylurea) has been found greatly to raise the threshold or completely to suppress electric shock and metrazol® convulsions in experimental animals and to be of low toxicity. The authors have now tested the drug on

90 patients with epilepsy of different types, all of whom had been resistant to the usual anticonvulsants. Fifty per cent were not significantly improved, and 50 per cent were rendered seizure free or were greatly improved, with the actions of the medication about equal against the three major types of attack. The effect on psychomotor epilepsy is impressive because of the relative failure of diphenyl hydantoin sodium U. S. P. and trimethadione in treatment of this kind of convulsion. The average dose given was 2.5 Gm. per day, and it was learned that if benefit was not derived from 3.5 Gm. per day larger amounts were also ineffective. The drug is tasteless and easily administered in the food for psychotic patients. Because it is rapidly eliminated, divided doses should be evenly distributed over the day. Common side effects were weakness and anorexia, but the most frequent complication was exaggeration of the preexisting personality disturbances which often accompany psychomotor epilepsy. This occurred in 20 per cent of patients, though incidence will, of course, depend on the prevalence of serious emotional imbalance in the specific group under study. In no patient without prior symptoms was a consequential psychiatric disorder precipitated, and a few patients showed improvement in psychologic status. Character difficulties were usually exaggerated only when psychomotor seizures were controlled, though in a few subjects personality disturbances broke out even if seizures continued. It is suggested that the ictal and nonictal components of the syndrome are independent, or even antagonistic. On withdrawal of Phenurone, attacks recurred promptly and the emotional disorder subsided, though in 1 patient there was no resumption of seizures and a severe psychotic state developed, which defied electric shock but yielded to subshock insulin therapy, whereupon psychomotor convulsions returned. Insomnia was present as a side effect in 6 per cent of subjects but was counteracted by phenobarbital or Mesantoin® (3-methyl-5-phenyl-5-ethyl hydantoin) which also seemed to give additional suppression of attacks. In 1 case hepatic disturbance, with jaundice, was conclusively traced to the use of Phenurone, and in 2 others there were evidences of transient renal damage. Only 1 per cent of patients showed a rash, and no effect on the blood was detected in any.

BEATON, Tucson, Ariz.

PANPARNIT® [CARAMIPHEN] IN TREATMENT OF PARKINSON'S DISEASE. ROBERT S. SCHWAB and DENIS LEIGH, J. A. M. A. **139**:629 (March 5) 1949.

Schwab and Leigh report the results of treatment of 50 patients with Parkinson's disease by means of caramiphen (panparnit®). Of these, 1 patient was treated over twelve months; 10 were treated over nine to twelve months, 9 over six to nine months, 22 for three to six months and 8 for less than three months. The results of treatment were evaluated on the basis of the (1) subjective report of the patient, (2) the report of a relative, (3) appearance and posture, (4) performance in daily life, (5) neurologic status, (6) electromyogram, (7) rate of movement and gait, (8) handwriting, (9) placebo and substitution effect and (10) opinion of an outside medical observer.

It was found that the best results were obtained by an overlap in the administration of the drug being taken with caramiphen, except in mild cases of the disease. Treatment is begun with as little as 12.5 mg. of caramiphen five times a day, in addition to the previous medication. The latter is then reduced slowly as the caramiphen is increased. This is accomplished by increase of the caramiphen in alternate doses, 12.5 mg. being given as the initial dose, 25 mg. as the next dose, and so on, on the second day. On the third day 25 mg. may be given five times daily. After four to five days the old medication is completely removed. The dose of caramiphen is then increased slowly until the mildest form of toxicity

is observed, after which it is reduced to a point at which side effects are absent or minimal. In a number of patients mild symptoms of overdosage will sometimes disappear if the schedule is maintained. No evidence of tolerance or addiction was found.

Caramiphen was found to be superior to previous drugs in 62 per cent of the patients; the degree of improvement was usually about 25 per cent. Sixteen per cent of patients were worse while taking the drug, and in the remaining 22 per cent the effect was similar to that experienced with scopolamine or stramonium.

Rigidity, in particular, is diminished, resulting in increased freedom and speed of movement. Tremor is diminished, but the change is less striking than with rigidity.

ALPERS, Philadelphia.

STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS; STREPTOMYCIN IN TUBERCULOSIS TRIALS COMMITTEE RESEARCH COUNCIL. G. MARSHALL and others, Lancet **1**:582 (April 17) 1948.

Marshall and his associates say that in September 1946 the Medical Research Council appointed a committee to direct clinical trials of streptomycin in the treatment of tuberculosis. This report is concerned with the results in tuberculous meningitis. The centers kept uniform records and followed general recommendations regarding dosage. The general results reported here refer to a total of 105 cases of the disease, as verified by culture, guinea pig inoculation or postmortem examination. A more detailed analysis is concerned with 92 of the cases. Of the 105 patients, 67 died; and of the 92 patients, 61 died. Of the 33 children under 3 years of age 27 died; of the 72 older children and adults, 40 died. Of the patients admitted at an early stage of the disease, 42 per cent were making good progress, as compared with 26 per cent of those admitted at a medium stage and 7 per cent of those admitted at an advanced stage. These figures indicate the great importance of early diagnosis. Of the patients who received streptomycin only intramuscularly, 11 per cent made good progress, as compared with 35 per cent of those receiving streptomycin by both the intramuscular and the intrathecal route. In patients who ultimately fared badly, tubercle bacilli were isolated from the cerebrospinal fluid much more frequently during the first three weeks than in patients who made good progress. Strains isolated from 22 patients between the twenty-ninth and the one hundred and thirty-sixth day of treatment were tested for sensitivity; only 3 of these were resistant to streptomycin.

J. A. M. A.

STREPTOMYCIN TUBERCULOUS MENINGITIS. D. L. GALLO, Semana méd. **55**:1057 (June 24) 1948.

Gallo reports the cases of 2 women aged 16 and 26, respectively, with tuberculous meningitis. Streptomycin was given by intraspinal and intramuscular injections. The younger patient received a total dose of 68 Gm. intrathecally and 78 Gm. intramuscularly. Clinical cure was attained, which has persisted more than one year after discontinuation of treatment with streptomycin. There are no pulmonary lesions. The older patient received a total dose of 64 Gm. intramuscularly and 3 Gm. intrathecally. Definite improvement followed, which lasted three months after discontinuation of streptomycin therapy. Acute symptoms, including symptoms of involvement of the central nervous system, appeared suddenly and terminated fatally. Necropsy revealed acute cerebral lesions. The author concludes that streptomycin is the only hope of cure for patients with tuberculous meningitis, the prognosis of which was hopeless before discovery of streptomycin and is now slightly, but favorably, modified.

J. A. M. A.

CEREBRAL PEDUNCULOTOMY FOR THE RELIEF OF INVOLUNTARY MOVEMENTS: HEMIBALLISM. A. E. WALKER, Acta psychiat. et. neurol. **14**:723. 1949.

Walker reports that section of the corticospinal tracts may eliminate the abnormal movements in athetosis, choreoathetosis, hemiballism and paralysis agitans. It has been established that the section may be made in the cortex, the internal capsule or the spinal cord. Cortical section on the left may result in aphasia, which represents an undesirable complication. The author, therefore, decided to section the cerebral peduncle because the pyramidal tracts are otherwise difficult to reach and section at this point leaves intact many extrapyramidal pathways which might be useful in retaining serviceable motor power.

He cites the case of a woman aged 49 who exhibited jerking movements of the right arm and leg and the right side of the face. The movements were rather violent, and any exertion increased their extent. They ceased during sleep and were diminished during rest. The movements of the extended arm consisted of abduction and adduction, with pronation and supination of the forearm and flexion and extension of the fingers. The actions were repeated two to three times per second. Rotary pelvic movements also took place. There were also abduction and adduction of the thigh and inversion and eversion of the foot of a frequency similar to that of the arm. Most of the laboratory tests and roentgenologic studies were noncontributory. However, the electroencephalogram showed an asymmetry in amplitude, with lowering of the voltage on the left side.

Walker decided to section the left cerebral peduncle. An incision 6 to 7 mm. in depth extended from the lateral sulcus medially for about 2 cm. It was estimated that the medial one fourth to one third of the peduncle was intact. Immediately after the operation there was complete right hemiplegia with cessation of the involuntary movements. Later, there followed internal strabismus with diplopia, but these soon subsided. Some power returned to the right leg, and the patient was able to walk, although the weakness in the right arm persisted. There were areflexia and hypotonia on the right side. The patient was discharged, but several months later she had to be treated for diabetic coma. Despite this, she had only few involuntary jerkings of the right hand. About one year after the operation the jerkings were still few, but they increased with emotional stress. Examination revealed reduced muscular power of the right hand and arm and fairly good muscular tone. The right leg had regained almost normal function. The author believed that the operation was successful in eliminating the hemiballistic movements.

PISETSKY, New York.

Muscular System

STUDIES IN DISORDERS OF MUSCLE: I. PROBLEM OF PROGRESSIVE MUSCULAR DYSTROPHY. F. H. TYLER and N. M. WINTROBE, Ann. Int. Med. **32**:72 (Jan.) 1950.

Tyler and Wintrobe point out that two types of progressive muscular dystrophy can be distinguished on clinical and genetic grounds: the childhood and the facioscapulohumeral type.

Dystrophy frequently is a genetically determined disorder. A peculiar pattern of muscular atrophy related to the age at which the anlage of a particular muscle appears in the embryo is found in progressive muscular dystrophy.

Creatinuria is the only well documented anomaly of metabolism which has been discovered to be associated with progressive muscular dystrophy. No other

data are available on which to start a search for the mechanism of the pathogenesis of this disease. The authors suggest that a good argument for the existence of a specific biochemical lesion in the metabolism of the involved muscle can be developed.

ALPERS, Philadelphia.

Diagnostic Methods

TRANSIENT HEMIPLEGIA ASSOCIATED WITH CEREBRAL ANGIOGRAPHY (DIODRAST). J. G. CHUSID, FRANKLIN ROBINSON and M. P. MARGULES-LAVERGNE, J. Neurosurg. **6**:466 (Nov.) 1949.

The authors report 2 cases of transient hemiplegia following the taking of cerebral angiograms with iodopyracet (diodrast®). In neither case was any sensitivity to the drug discovered with the ocular test. In case 1 complete flaccid hemiplegia of the left side appeared. With treatment with tetraethylammonium chloride, given intravenously, the hemiplegia disappeared in two and one-half hours. In case 2 flaccid hemiplegia of the right side developed after the injection of 35 per cent iodopyracet solution into the left carotid artery. Two hours later the power of the right lower extremity was regained, and four days later there was complete recovery of speech and motor powers.

It is the opinion of the authors that the hemiplegias were due to spasm of cerebral arteries and that the recovery of their patients was influenced by the use of tetraethylammonium chloride.

In a careful review of the literature, they failed to find any report of transitory hemiplegic phenomena due to the use of iodopyracet in cerebral angiography.

TOZER, Philadelphia.

Encephalography, Ventriculography and Roentgenography

CONVOLUTIONAL MARKINGS IN SKULL ROENTGENOGRAMS OF PATIENTS WITH HEADACHES. L. M. DAVIDOFF and H. GASS, Am. J. Roentgenol. **61**:317 (March) 1949.

Roentgenograms were made of the skull of 100 consecutive patients with headache. These were compared with 100 roentgenograms of healthy subjects in the same age and sex distribution. There was no significant difference in the incidence of convolutional markings in the two groups. The authors found that the convolutional markings may occur without pathologic significance in the third, fourth and fifth decades, more commonly in women.

TEPLICK, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Sherman F. Gilpin Jr., M.D., *Presiding*

Regular Meeting, Nov. 26, 1948

Virulent Virus Infection of the Central Nervous System, with Xanthochromic Spinal Fluid and Bizarre Pellicle Formation: Report of a Case. DR. SAMUEL A. ZERITSKY.

A clinical experience in virulent disease of the central nervous system, fatal in its outcome, despite a *Blitzkrieg* of therapeutic tactics, was reported, together with a brief review of the occurrence of xanthochromia in neurologic disorders. Intracerebral inoculation of mice with the patient's spinal fluid having failed to identify the offending organism, the alternate possibilities of differential diagnosis were discussed.

REPORT OF CASE

An attractive white girl, 19 years of age and the only child, had been in excellent health until the abrupt onset of her illness, on Aug. 14, 1948. On arising as usual, she complained of generalized joint pains and was found to have a temperature of 100 F., which later in the day rose to 103 F. The following day she appeared to become toxic, vomited and continued to have fever, with a temperature fluctuating from 100 to 104 F. On August 16, her condition having become more serious, her physician sent her to the hospital with a tentative diagnosis of virus pneumonia.

Course in the Hospital.—No indication of the possible cause was evident on physical examination at the time of her admission. There was no nuchal rigidity, Kernig sign, cutaneous rash or purpura. An emergency roentgenogram of the chest eliminated the lungs as the site of the disease process. A cell count was reported as 13,000 white cells, with 61 per cent segmented and 18 per cent nonsegmented granulocytes, 19 per cent lymphocytes and 2 per cent monocytes. Shortly after her admission blood was taken for culture and was reported to show no growth after twenty-four hours. That evening she had a chill; her temperature rose to 106 F., and she was irrational. By the following morning, August 17, she was semilethargic and resembled a person in shock. Administration of duracillin® (compound of penicillin G and procaine hydrochloride suspended in sesame oil), penicillin and adrenal cortex extract; intravenous injections of dextrose solution, and a mixture of oxygen in air, soon supplemented by a blood transfusion and even streptomycin, were all ineffectual. At this time an examination of the spinal fluid, made without difficulty, revealed xanthochromic fluid, in which a funnel-shaped pellicle formed within a few minutes. Centrifugation of the specimen did not in any way affect the amber color. There were no red blood cells, crenated or otherwise, in the fluid, which was reported to contain 2 white cells per cubic millimeter. The total protein measured 82 mg., the glucose 84 mg. and the chlorides 640 mg., per hundred cubic centimeters. Studies of the smear and culture were subsequently reported as revealing no organisms.

Neurologic examination made after the spinal puncture revealed that she was in a somnolent state but could usually be aroused. The deep reflexes were diminished throughout; yet a distinct Babinski sign was obtained on the right side. During the examination convulsive movements appeared, involving first

the left side of the face, and then the left shoulder, thumb and index finger. These movements lasted about a minute and were repeated several times that day. Her lethargy and somnolence progressed ominously; some twitching movements of the right upper extremity were noted, and the peripheral circulatory collapse became irreversible. Shortly after midnight she died, the total period of her illness being just three and one-half days.

Comment.—Thirty-six conditions responsible for xanthochromic cerebrospinal fluid have been noted in a review of the literature; they range from jaundice, with a yellow fluid in about 15 per cent of cases, through subarachnoid bleeding, attributed to the breakdown of hemoglobin, and, finally, epidemic encephalitis, radiculitis and Guillain-Barré syndrome. Oppenheim, many years ago, described toxic hemorrhagic encephalitis, which Baker (1935) designated as a nosologic entity; for this he suggested the term toxic hemorrhagic encephalopathy. Summaries of this condition, presented by Grinker and Ford in their textbooks, describe the spinal fluid as being frequently bloody, but often normal (making no mention of xanthochromia as such). The present case could very properly fit into the profile of clinical descriptions presented for this disease, which diagnosis is, therefore, offered as the alternate choice for those who are disinclined to accept a virus etiology in the face of the absence of demonstrations of any organism.

DISCUSSION

DR. FRANCIS M. FORSTER: Dr. Zeritsky has pointed out that he is not certain of the disease entity in this case, and has discussed a host of possibilities in differential diagnoses. Why does he not more seriously consider thrombosis of a dural sinus?

DR. E. A. DENBO, Camden, N. J.: Was there any clinical evidence of jaundice? Was the icterus index determined?

DR. SAMUEL A. ZERITSKY: I mentioned the possibility of dural sinus thrombosis—nonseptic thrombosis—as an occasional cause of xanthochromia. In this particular case, although the possibility was considered, there were no localizing signs of sinus thrombosis, as opposed to the alternative diagnosis of toxic hemorrhagic encephalopathy. I may mention parenthetically that the negative report for virus infection does not in itself throw out the diagnosis of virus disease, to which I personally gave major consideration.

As to the question of jaundice in this case, there were certainly no clinical signs of icterus. The cases of jaundice mentioned in the literature associated with xanthochromic spinal fluid did not exhibit involvement of the central nervous system. I included that classification merely for completeness.

A New Instrument for Performing Transorbital Leukotomy. DR. MATTHEW T. MOORE.

Fiamberti (*Rassegna di studi psichiat.* **26**:797-805, 1937) devised an ingenious method of severing certain frontothalamic fibers by means of a transorbital approach. His simple procedure eliminated many of the disadvantages inherent in the orthodox transfrontal leukotomy (lobotomy), topectomy and frontal lobectomy in the treatment of intractable cases of some of the psychoses and psychoneuroses. The method was adopted in this country by Freeman (*Lancet* **2**:371 [Sept. 4] 1948), and, because of the device employed, it has come to be known as the "ice pick operation." In order to remove the stigma of such an unattractive term from what may prove to be a valuable advance in psychiatric treatment, and to overcome the defects of the ice pick, which has the appearance of a crude

weapon rather than of an instrument, the transorbital leukotome here described has been devised; this instrument provides superior and safer performance.

The defects of the ice pick are as follows: 1. It lacks balance. 2. Because of its round cross section and absence of gradual increase of caliber, it is easily "lost," or "runs," when struck with the mallet. 3. It affords no means of visualizing the anatomic position of the tip in the brain. Because of these serious defects, the ice pick can slip away from the guiding hand of the operator and be thrust too deep into the brain, or the point may, during the lateral sweep of the handle, be carried too far mesially and rupture the anterior cerebral artery or the pial arteries, with resultant serious hemorrhage.

The transorbitome is so constructed that it obviates the foregoing disadvantages. The shaft, in cross section, is elliptic and has a gentle increase in caliber from the point to the hilt, thus providing a "set," when forced through the orbital plate, and preventing "running" when struck with the mallet. Moreover, the shape of the shaft permits easy removal, in contrast to the occasional wedging or sticking of the ice pick in the orbital plate. The extension arm, when the handle is maintained in the horizontal plane, affords direct visualization of the mediolateral movement and position of the tip of the transorbitome within the brain. The distribution of weight in the shaft and handle makes for a balanced, easily manipulated instrument.

The instrument is introduced in the same manner as that described by Fiamberti and by Freeman. It then is forced inward to a position which brings the 4 cm. mark in apposition with the rim of the upper eyelid; the handle then is swung laterally, so that the tip of the extension arm moves 1 cm. mesially; the instrument is then brought back parallel to the midline and forced inward to the 7 cm. mark; the handle then is swung laterally so that the tip of the extension arm moves 2 cm. mesially, but not beyond a point 1.5 cm. lateral to the midline, thus avoiding section of pial arteries and the anterior cerebral artery; the handle of the instrument then is moved mesially so that the tip of the extension arm is at a point 1 cm. lateral to the parallel line of insertion; finally, the transorbitome is brought back to the parallel position and withdrawn. If more extensive sectioning of the white matter is desirable, cuts can be made with the instrument at the 5 or 6 cm. mark.

DISCUSSION

DR. HERBERT FREED: Dr. Moore is to be congratulated on giving us a lucid demonstration of a new instrument and a relatively new technic.

Our attitudes have changed with respect to the shock therapies. For example, when I first began to give convulsion therapy with camphor and metrazol® in 1938, I remember how some of the men on the staff of Philadelphia General Hospital shuddered when they saw a patient going through a severe convulsion; now, they would think nothing of having a patient undergo the same procedure.

Without Dr. Moore's going into details as to what he has accomplished with the treatment, I should appreciate his giving his morbidity and the mortality rates for this procedure.

DR. CHARLES RUPP: I should like to ask Dr. Moore whether he has noted any injuries of the eye itself other than the subconjunctival ecchymosis, and whether he has encountered any bleeding within the intracranial cavity.

It has been suggested that this procedure is safe in the hands of the psychiatrist. I know of a case in which the operation was done by a psychiatrist according to the classic Freeman technic. Something went wrong; the ice pick penetrated the frontal sinus and came out on the forehead. I wonder whether that has occurred in any of Dr. Moore's operations.

DR. SAMUEL A. ZERITSKY: The acceptance or rejection of this procedure should be based entirely on the feasibility of the maneuver and its purpose, not on which category of medical specialists has a lien on its use. At this stage of its consideration, one is not concerned with whether it is to be the neurosurgeon, the neurologist or the psychiatrist who is qualified to perform it. Emotional bias has no place in a truly scientific consideration, and the advisability of including transorbital leukotomy in the armamentarium of the psychiatrist must ultimately be based on principles.

DR. MATTHEW T. MOORE: Dr. Freed has sounded a note of openmindedness which has so frequently been absent when a new modality is introduced into the field of medicine, and especially is this so in psychiatry. Until the advent of narcohypnosis, metrazol® convulsion therapy, electric shock therapy and the various types of psychosurgery, psychiatry had been essentially a verbalizing branch of medicine. It was not until these new methods were introduced that neurosurgery has actually been able to offer something practical and productive of tangible results. I recall well during the early days of metrazol® that many, including myself, looked on the terrifying procedure in horror. Today, however, it is recognized that in properly selected cases shock therapies, especially electric shock therapy, literally works miracles. So it is with psychosurgery—in this case, transorbital leukotomy. The neurosurgeon must proceed cautiously in utilizing such a method and be certain of the indications for it before applying it. On the other hand, it should not be condemned without proper trial. The advantages of transorbital leukotomy over the orthodox prefrontal lobotomy are the ease of performance, the fact that the patient does not require lengthy hospitalization, the absence of deterioration of personality and behavior, so frequently encountered in prefrontal lobotomy, and, finally, the important factor of a relatively small economic outlay, as compared with the orthodox procedure.

In answer to Dr. Freed's question, my colleagues and I intend to present the results in our cases after we have had a sufficiently large series of patients and a proper amount of time for evaluation of the results. Dr. Walter Freeman has informed me that he has used the procedure in over 180 cases and has had no deaths. In 3 cases he has had cerebral hemorrhage resulting in temporary hemiplegia, which has cleared up. The results of his studies have indicated improvement in approximately 80 per cent of cases.

Jones and Shanklin reported similar results in 73 cases. One death has been reported in the literature thus far. We have operated in 55 cases to date and have had 1 death. Among the 54 living patients there has been no morbidity and no complications of any type. The patient who died had a focalized cerebral hemorrhage in an area of softening. He had had mild hemiparesis, but, in view of the fact that he was suicidal, extremely agressive and a serious concern to his family, it was felt advisable to carry out the procedure. The hemorrhage was in the left frontal lobe and was confined entirely to the subcortex. No large vessels were involved. Briefly, I may say that our results thus far parallel those of Freeman and of Jones and Shanklin.

In reply to the question concerning the penetration of the frontal sinus, I can merely say that the operator undoubtedly had not placed the point of the instrument well up into the vault of the orbital plate, and that the instrument was incorrectly directed. I have had roentgen studies of these cases, and the perforations are situated well beyond the posterior wall of the frontal sinus, and in no case has there been penetration of the frontal sinus. If the procedure is carried out as I have shown in the slides and in the motion picture, there should be no difficulty.

Wave and Spike Discharges in the Electroencephalogram. Dr. Francis M. Forster and Dr. Arnold Allen (by invitation).

The purpose of this study was to examine the various components of the electroencephalogram showing wave and spike formations in the 3 per second range. Two hundred consecutive electroencephalographic records showing this type of discharge were studied. The results showed that the wave and spike formation usually occurs on the background of a normal basic cortical rhythm, and that it is remarkably constant in its occurrence in a frequency range of from 2.5 to 3.5 cycles per second. However, considerable variation in the position and amplitude of the spike component appear in the same record, and, indeed, within the same discharge. Wave and spike formations are seen most frequently during hyperventilation. Other paroxysmal disturbances occur in 50 per cent of the records, the most frequent of these being single or multiple spiking discharges and paroxysmal bursts of 4 to 6 per second activity. A surprisingly high incidence of wave and spike formation occurs after the age of 30 years. Various theoretic considerations of these results are discussed.

DISCUSSION

Dr. Charles Rupp: In the cases in which clinically the grand mal seizure pattern was replaced by a petit mal pattern, were there corresponding changes in the electroencephalogram, with the appearance of a wave and spike formation?

Dr. Samuel A. Zeritsky: Does Dr. Allen mean to state that each time a spike and wave pattern appears in an electroencephalogram the patient, if he has a true petit mal, will exhibit a petit mal attack? I understood Dr. Allen to say that he would not consider the case as one of petit mal unless a clinical attack occurred simultaneously with each spike and wave pattern.

Dr. Matthew T. Moore: Has Dr. Allen obtained sleep patterns in the electroencephalogram; if so, are these patterns similar to the waking ones?

Dr. George D. Gammon: If one spike and slow wave formation does not result in an attack, how many are required to produce a seizure? Is the number of spikes and slow waves the sole determining factor in causing an attack?

Dr. Alexander Silverstein: Have the authors any data as to what percentage of their patients with clinical petit mal showed a normal electroencephalographic pattern?

Dr. Francis M. Forster: Dr. Gammon asks what determines whether the patient will have a seizure. I wish we knew. That is the crucial question in the whole problem of the etiology of epilepsy. Wave and spike formation occurs rarely in persons who have no family history of epilepsy. In cases of idiopathic epilepsy wave and spike formations are the clearest cut patterns in the electroencephalographic tracings.

We were surprised at the age range. Since this series of 200 cases was closed, we have seen wave and spike discharges in a patient aged 63.

Some years ago, when Dr. Lennox was pointing out the necessity of breaking up the types of minor seizures in the diagnostic categories of petit mal and psychomotor attacks, the differentiation was considered by some an academic question. The development of electroencephalography corroborated the clinical impression of a difference between petit mal and psychomotor seizures. The need of differentiating petit mal and psychomotor seizures is now obvious, for the treatment is different.

It is not always possible clinically to be certain of the seizure type, however. There are occasionally patients with prolonged confusion states. For instance, a 38 year old patient in our clinic recently had occasional grand mal seizures and periods of confusion lasting three days, always associated with the menses. It was difficult to determine whether this was a "dreamy" state. Electroencephalograms taken in the confused state showed that this woman was in petit mal status.

An occasional patient with grand mal seizures becomes much worse with use of diphenylhydantoin, despite care in the transition to its use, and the electroencephalographic record at that time often shows runs of wave and spike formations. The inference is simple, namely, that the diphenylhydantoin has precipitated the petit mal discharges, which in that patient are the precursors of the grand mal seizures.

This series of 200 patients was restricted to those with wave and spike discharges which were bilaterally synchronous. This type of discharge is indicative of idiopathic epilepsy. There is a difference of opinion as to whether the discharges from the two hemispheres are truly synchronous. Recently, by studying these formations on cathode ray oscillographs, Cohn has shown that there is a slight dyssynchrony, the lead of one hemisphere over the other being in the millisecond range. How those slight differences will be explained, no one knows as yet.

Occasionally, after injury one finds unilateral focal petit mal discharges. That is quite outside the province of this paper. The condition is extremely rare.

I wish to stress again the importance of the fact that these wave and spike discharges were seen with normal basic rhythms, and that therefore adequate hyperventilation is most important.

DR. ARNOLD ALLEN: In answer to Dr. Rupp's question: The changes in the case of petit mal were apparent clinically as well as in the electroencephalogram.

In answer to Dr. Zeritsky's question, "Is a clinical attack necessary for the diagnosis of petit mal?" I think the answer is "Yes." In the absence of a clinical attack one may assume that the patient may have petit mal, but one cannot say he does unless he has clinical attacks.

Dr. Moore asked about sleep records. We have not often taken sleep records in cases of petit mal epilepsy. It has been our experience that in taking hyperventilation records during fasting we have obtained fairly good results, and we have never had to resort to sleep records.

DR. FRANCIS M. FORSTER: I should like to add one comment: The sleep record requires several hours of continuous running, and the tracings in these 200 cases were gathered over a period of about a year and a half to two years. Because of limitations of time, we cannot take routine sleep records. The sleep records we are obtaining are from patients of one of two groups: patients who are assumed to have idiopathic seizures and whose resting records are normal, and patients who suspect a focal lesion and whose records reveal no focus.

Rudolph Jaeger, M.D., *Presiding*

Regular Meeting, Feb. 25, 1949

Effect of Poliomyelitis on the Function of the Motor Neuron. DR. D. DENNY-BROWN, Boston.

The advocacy of various forms of treatment of poliomyelitis in recent years had emphasized features of the disease which were little understood. Any discussion of treatment involved questions as to the natural manner of recovery of damaged motor neurons, of which literally nothing was known. Dr. Brown's conclusions from a series of electromyographic studies of human and animal poliomyelitis, in collaboration with Dr. J. M. Foley, were presented.

In the beginning, a clear distinction had to be drawn between reflex spasms of flexor muscles in the limbs, due to a protective reflex in the spinal cord, and a true enhancement of the postural stretch reflexes in the muscles. The former, of which Kernig's sign is an example, are not associated with increase in the tendon reflexes and, when present, may last for many weeks. Enhancement of postural stretch reflexes also occurs in poliomyelitis, is mild and generalized in both flexor and extensor muscles, is associated with increase in the tendon reflex if enough neurons are still active and is a transient feature, beginning in the preparalytic period and lasting from one to three weeks. It was never, in the author's experience, sufficiently intense to cause spasticity comparable to hemiplegia or spinal spasticity, though a clonic tremor was sometimes part of it. Because of its presence, a few surviving units in an otherwise paralyzed muscle could be activated more easily by stretch than by other means.

In paralyzed muscles residual partially affected motor units could commonly be found by electromyography. By their unusual rhythms of discharge, partially damaged motor units could also be detected in muscles only slightly weakened. In the first three weeks after the onset of paralysis, such motor units had a very slow, irregular and easily fatigued motor discharge. Coupled beats, followed by pauses, were common, and in a few instances grouped series of beats of high frequency, followed by long pauses, occurred. From the third week on, the discharge rhythms became gradually more regular but were interrupted by doubled beats. These became gradually less frequent, and after six to nine months the discharge rhythm had become completely regular. New units appeared in previously silent portions of muscle during convalescence and underwent the same slow recovery of normal rhythm of discharge. No new units were observed with certainty after the first three months. These recovering motor units had a higher threshold than other, normal units in the same muscle and were brought into contraction with less effort later in recovery. In a severely paralyzed muscle increased willed effort caused a marked acceleration of the rate of discharge in residual but normal units. There was no change in the estimated size of motor units remaining in the muscle, and hence no reason to suppose that regeneration occurred. Fibrillation, when present, appeared to denote irreversible damage to the motor neuron.

A study of the whole course of the disease in monkeys by electromyographic methods disclosed that an abnormality in discharge rhythms was the first sign of the disease, preceding fever and paralysis by as long as three days. The change was seen as doubling and trebling of the beats of discharge in high threshold motor units and soon involved most of the motor center of a region. It was then associated with increase in all reflex discharge from the center, including the stretch reflex. The irregular clonus of the latter reflex caused the tremors of the preparalytic phase. Immediately preceding paralysis the affected units discharged in bursts of higher frequency, and the last discharges recorded before necrosis of the anterior horn cells were brief bursts of 3 to 50 beats at a rate of 240 to 350 a second. In muscles in which paralysis did not occur, reduplication of high frequency beats continued for two to three weeks and gradually reverted to normal rhythms. Residual and recovering units in areas of almost complete paralysis behaved as in the human muscle. After twenty-six days, in 1 animal little abnormality in discharge remained, and then only as occasional reduplication of beats. Sections of the corresponding segments of the spinal cord showed, among the surviving motor cells, besides a majority of cells of normal appearance, approximately 20 per cent hyperchromatic cells, and a few cells still mildly chromatolytic. In

another animal the electromyogram still exhibited gross reduplication of beats after sixty-seven days. The corresponding gray matter showed only a few hyperchromatic cells.

The diffuse initial disorder of discharge rhythm of the motor units and the long delay in its restoration appear to be more sensitive than the reported histologic change as an indicator of the cellular damage in poliomyelitis. That the initial effect is an increase in frequency of discharge strongly suggests that the disease primarily affects part of the excitatory mechanism of the motor cell. There was close similarity between the action of strychnine and tetanus toxin on the motor neuron and the first effect of the poliomyelitis virus. The reflex changes in the preparalytic period also closely resembled the effect of these substances and was not that seen in damage to the reticulum of the brain stem. The myotatic changes were a local motor toxic effect, and not a release phenomenon.

The implications of these observations in relation to current theories of treatment were briefly discussed.

DISCUSSION

DR. FRANCIS M. FORSTER: In the use of a double wire in a concentric needle, is it possible to avoid picking up distant motor units? Second, does Dr. Denny-Brown feel that it is possible to identify these extraneous units with fair facility?

DR. F. H. LEWEY: How were the monkeys made to move? Or were the records stretch electromyograms? I have seen the 1,000 microvolt motor units in reinnervated muscles after nerve section and suture; however, I have never seen them in normal persons, even on extreme effort. What is the rationale of using a very high frequency galvanometer instead of an oscilloscope?

DR. JAMES RYAN: Did any of the animals show fasciculations? Why does one not see fasciculations in patients with poliomyelitis more frequently?

DR. GEORGE GAMMON: I was interested in Dr. Denny-Brown's analogy of poliomyelitis and tetanus; but I did not quite understand whether he drew an analogy between the two conditions and a low calcium level. Harvey, in studying the effect of tetanus antitoxin, called attention to the similarities of the neural discharge in cases of low calcium and in those of tetanus.

I should also like to ask whether the author has encountered the phenomenon which Dr. Hodes described from his studies on late poliomyelitis, in which he occasionally observed a sort of myasthenic decline in the size of the potential from single units—in that case, I believe, from electrical stimulation of peripheral nerves—and which he showed to be partially reversed by neostigmine, though not to the same degree as in the case of myasthenia gravis.

If the condition of excessive discharge leads to failure of contraction in poliomyelitis, can drug therapy of any kind influence this condition sufficiently to make it a worth while clinical undertaking? In other words, can you reverse this hyperexcitability by any of the drugs or other methods available? I have the impression that one of the effects of heat therapy may be just that. I should like to know whether Dr. Denny-Brown finds it so.

DR. ALEXANDER SILVERSTEIN: I should like to ask Dr. Denny-Brown whether he can give us a simple explanation of the so-called spasm in poliomyelitis and whether he has carried out similar studies in cases of the nonparalytic phase of poliomyelitis, the only symptoms of which are increased tension of the posterior muscles of the neck and impairment in straightening the leg (Kernig's sign). In these cases the spinal fluid often shows pleocytosis, the count being as high as 200 to 300 cells per cubic millimeter, with predominance of granulocytes, the latter changing within forty-eight hours into a predominance of lymphocytes. What is

the mechanism of these so-called meningeal signs at this stage of poliomyelitis? I did not hear Dr. Denny-Brown mention the internuncial neurons, which, according to some enthusiastic observers, are said to be related to the "spasm."

DR. DENNY-BROWN, Boston: In answer to Dr. Forster's question as to whether a double electrode would not be more satisfactory: I can only say that my colleagues and I have tried all kinds of electrodes and that we always come back to an earthed needle with single core. The double electrode is excellent for some purposes. So, also, is a single electrode with a grounded surface lead, as used by Jasper, but it tends to sample a much larger area of muscle. If one wants a single unit discharge in a muscle in which there are many other units discharging—in other words, if one wants to localize the exploration—a single lead inside a grounded needle is far superior to any other.

The oscilloscope, of course, is a more faithful recorder than the galvanometer type of oscillograph. The difficulty with the oscilloscope lies in (1) taking a continuous record for a long period, and (2) combining it with any mechanical record. For the type of study I have described, one seldom needs a mechanical record, but if one wants to find, for instance, the relation of the tremor of a muscle to the behavior of the muscle units, it is much easier to bring the beams from the galvanometers and a manometer to the same piece of moving bromide paper with an oscillograph than it is to combine the mechanical record with what is seen on the oscilloscope tube.

We found that throughout the acute stage of poliomyelitis the stretch reflex in the muscles was much the easiest way of getting a grade of contraction that could be reproduced over and over again in a given muscle. As an alternative, in the case of a quadriceps muscle, one can make the animal stand up with the electrode in place and so get him to innervate the muscle. Grasping with the hand or foot is not difficult to elicit in most monkeys. Our conclusion was that we could activate more muscles by stretching than by voluntary activity. There are several difficulties to be avoided. The monkey has a peculiar kind of jerk which he makes as an aggressive movement. On the electromyogram, such a jerk has the appearance of a high frequency burst. Actually, it is a number of units discharging briefly at about 50 beats a second. This discharge might be mistaken for a high frequency burst, which is the typical disorder of poliomyelitis. It was common to see little flickerings in the muscle, confined to one part of the muscle, with attempted activity of the animal, and these fasciculations correlated with the presence of high frequency bursts.

The large units which are found in the convalescent stage are, I am sure, present in normal muscle. Granted that the twitches which are called fasciculation in amyotrophic lateral sclerosis are single discharges in single motor units, it is obvious that there are different sizes of units, for there are different sizes of fascicular twitchings in that disease. There are all sizes of twitches in one muscle, and therefore there must be all sizes of motor units in one muscle. In voluntary movement we habitually begin normal contraction with small units. Therefore, the big ones must come in at the height of contraction.

After regeneration from damage to a peripheral nerve, active muscle fibers are scattered through the muscle, and some of them receive their nerve impulse rather later than others of the same unit, giving a polyphasic action potential. Histologic study of such muscle shows long threads of regenerating nerve fiber wandering to reach muscle fiber at a considerable distance from the main body of the unit. That type of action potential, or histologic feature, is not seen in cases of poliomyelitis. We found no reason to believe that there is regeneration of nerve fibers in poliomyelitis. Even after nerve injury the number of fibers a motor axon will innervate seems to be limited.

Some therapies for poliomyelitis are based on the notion that there is something regenerating in the muscle. The only change we have noted in regeneration of the muscle is increase in the sarcoplasm of atrophic fibers. The fiber enlarges as it takes up activity again. When, for example, a whole muscle was completely paralyzed in a monkey, except for the recent return of electromyographic discharge in two units, these units could be localized with fair accuracy with the needle electrode, and histologic examination showed a little group of muscle fibers which were smaller than normal, but which were not degenerated. Such a little group of muscle fibers showed the change which one calls the atrophy of disuse. This all tends to show that in poliomyelitis the inactive neuron is anatomically intact, and that the process of recovery is taking place at the cell membrane, and in the nuclear apparatus of metabolism.

In poliomyelitis, there is an extraordinary excitability of some muscle fibers early in the disease, so that the mechanical stimulation of the needle stimulates bursts of fibrillation. This may be only an early phase of the fibrillation of atrophy; but it sometimes occurs too early for that and so we are not sure of its significance.

Dr. Gammon asks whether the high frequency bursts resembled the effect of low calcium levels. The electromyographic discharge is different, though it also is a repetitive burst.

That brings me back to Dr. Silverstein's question: What is spasm? I have difficulty in understanding what others mean by the term, but I should say this: In poliomyelitis, if it is found that there is, let us say, foot drop, the gastrocnemius muscle is firm and contracted, and often every attempt to dorsiflex the foot meets with resistance and pain. If passive dorsiflexion is continued long enough, just within the limit of severe pain, such resistance can be overcome. This resistance is very commonly encountered in clinical neurology. One does not ordinarily call this "spasm," for there is no muscular activity until the passive movement is made. The condition occurs with any kind of immobilization of innervated muscle and is not peculiar to poliomyelitis. It is the process that underlies contracture. It is a very important clinical phenomenon, and it can lead, as Sister Kenny maintains, to deformity. It can be counteracted by local heat and prevented by avoiding malposture, but I find it difficult to believe that the best treatment for it is the poisoning of neural transmission in a disease primarily caused by disorder of transmission.

After experimental ischemia of the spinal cord there is damage to motor neurons in the intermediocentral group, severer than to those in the peripheral gray matter, and in these circumstances the limb certainly becomes spastic. That appears to be because the multiple internuncial pathway for pain reflexes is interrupted and the single reflex relay for proprioceptive reflexes is left undamaged. In spinal reflexes there is always a balance between the two, but I do not think that happens in poliomyelitis. If it did, the limbs would remain spastic longer and the tendon reflexes would be uniformly overactive. The altered stretch reflex in poliomyelitis thus differed from that which is found after ischemia of the spinal cord.

Muscular spasm is therefore a complicated subject. One variety of it is contracture; another is obviously what is called the meningeal reaction, and yet another development of it, which I think has been entirely overlooked, is the mild generalized, transient increase of stretch reflexes which I have described this evening.

What one is looking for, of course, is something objective by which to measure, to gage, the progress of the damage caused by poliomyelitis and its recovery. If one knows the reactions of a nerve cell damaged by poliomyelitis, if one knows its general behavior, then one can say whether local heat, or neostigmine, or whatever, makes any difference to it. One is not yet in a position to say that.

Rudolph Jaeger, M.D., *Presiding*

Regular Meeting, March 19, 1949

Neurosurgical Procedures for Preservation of Vision in an Adult with Acrocephaly: Report of a Case. DR. R. L. LEOPOLD (by invitation), DR. M. D. RAIFORD (by invitation) and DR. L. L. ADAMKIEWICZ (by invitation).

Since a review of the literature failed to reveal any cases in which neurosurgical methods were employed to alleviate symptoms arising from acrocephaly, a case was presented in which arterial ligation was helpful in preserving failing vision.

REPORT OF CASE

A white man aged 49, who was right handed, was first seen because of headache of six to eight months' duration and diminution of vision for an undetermined period. These headaches were increasing in frequency and were severe and bilateral. He also complained of ringing in the right ear and of infrequent periods of syncope. The headaches were made worse by eyestrain, but there was no history of nausea or vomiting.

He had had an injury to the left eye early in life and had never had useful vision in that eye. He had been known to have mild diabetes for many years.

Examination revealed a short, well developed man with a tower-shaped skull. The presence of acrocephaly was confirmed roentgenographically. Physical and neurologic examinations showed nothing remarkable except for the ocular condition. Vision in the right eye on Sept. 13, 1947 was 6/15 uncorrected and 6/9 corrected. Only light perception was present in the left eye. There was bilateral exophthalmos. Ophthalmoscopic examination showed the right disk to be pale and sharply outlined. The left disk was white. The visual field of the right eye was greatly constricted. The ophthalmologic diagnosis was that of bilateral optic nerve atrophy and bilateral exophthalmos.

From the patient's old records, made available by several physicians, it was apparent that, whereas the loss of vision in the left eye had been permanent, that in the right eye was progressing.

In view of the loss of vision and the headache, an exploratory craniotomy was performed by Dr. Robert A. Groff. The dura was tightly adherent to the bone. The right internal carotid artery was not easily seen; when located, it was felt to be pressing tightly on the right optic nerve, and the beginning of the ophthalmic artery could be seen lying next the optic nerve, just behind the anterior clinoid process. A similar situation was found on the left side. The left optic nerve was atrophic and smaller than normal; in contrast, the right optic nerve appeared normal despite the fact that the artery was seen pulsating directly against it. The right internal carotid artery and right optic nerve were freed and the structures separated by blunt dissection. The wound was closed in the routine manner.

The postoperative course was satisfactory, and digital compression of the right internal carotid artery was performed daily. On the eighth postoperative day the right common carotid artery was ligated in the neck. Nine hours later the patient had a mild generalized convulsion, and within thirty hours left hemiplegia developed. The craniotomy wound was reopened, and a thick epidural clot was found and evacuated. This opportunity was taken to reexamine the chiasmal region, and the right internal carotid artery was observed to be pale and soft, and not to pulsate.

The hemiplegia regressed rapidly, and no further convulsions occurred.

The patient has been followed at monthly intervals. When he was last seen, in May 1948, his corrected vision was 6/9. He was free of headache, was ambulatory and had returned to work.

Pathogenesis of the visual loss associated with acrocephaly has never been clearly demonstrated. Until 1938 various surgical technics were used to preserve vision, either by decompression or by widening the optic foramen. Failure was general. In 1938 King reported good results with his "morcellation" technic, but this is a method which is useful only in children.

In the present case, it is postulated that the prefixed optic chiasm and the anomalies of the internal carotid arteries and the optic nerves were the result of the unusual configuration of the skull. Over a period of years adhesions had developed between the nerve and the artery, producing gradual compression of the optic nerve, with resultant progressive loss of vision. Craniotomy was performed, and the unique opportunity afforded the neurosurgeon at the time of the reexploration to evaluate the operative result gives hope that a good lasting result may be expected.

DISCUSSION

DR. A. M. ORNSTEEN: In speaking of the operation for the preservation of vision in acrocephaly, are the authors talking about decompression of the cranium? If so, what about the case in which there is progressive impairment of vision with the artery pressing on the optic nerve? In the present case the common carotid artery, I believe, was ligated in the neck on one side, and decompression was also done—am I correct?

DR. R. L. LEOPOLD: No, no decompression was done. The craniotomy wound was closed without decompression.

DR. A. M. ORNSTEEN: What is the relation of the acrocephaly and the pressure on the optic nerve by the internal carotid artery? I ask that because the other day I saw a man whose right optic nerve seemed to be compressed by a tortuous carotid artery which did not appear calcified in the roentgenogram. He had a superior altitudinal hemianopsia and atrophy of the lower half of the optic nerve. He did not have acrocephaly; he was 59 years of age. The loss of vision came on rather suddenly, on January 27. Because of the pallor of the lower half of the right optic nerve and the normal color of the upper half, the normal color of the left optic nerve and a Wernicke pupil (no response to light stimulation of the lower half of the retina and feeble response when the light is thrown on the upper half), I believe he has an aneurysmal dilatation or a tortuous carotid artery, which passes under the optic nerve and compresses it from below.

If the case of acrocephaly reported, compression of the optic nerve by the internal carotid artery was relieved by ligation of the common carotid artery; what is the connection between acrocephaly and the pressure on the nerve by the artery with relation to this patient I have just seen who had no acrocephaly? Is it acrocephaly, or is it an anomalous artery with no relation to the acrocephaly?

DR. FRANCIS GRANT: May I ask the authors why the left nerve was not involved? If that nerve was closely compressed by the artery, as shown in the illustration, and if this man begins to have difficulty with his left eye, will they ligate the left carotid artery, too?

DR. RUDOLPH JAEGER: I was wondering whether this man's acrocephaly had anything to do with the arterial pressure against his optic nerve. This situation is fairly frequent in arteriosclerosis of the internal carotid artery. The vessel enlarges, elongates and pushes up against the optic nerve. This is aggravated by the fact that the ophthalmic artery comes off at a right angle to the carotid and the turn of this vessel pushes directly up into the optic nerve.

Several years ago I treated a girl with just this condition, but without acrocephaly. The carotid artery pressed tightly against the optic nerve, and I took off the roof of the optic canal, thereby permitting the carotid artery to push upward without exerting pressure against the nerve. Three or four years later it was necessary to perform the same operation on the opposite side, permitting retention of vision.

The other day I noticed that Dr. Tassman had recently reported a case in which I did the same thing about three years ago on a patient at Wills Hospital. In Dr. Tassman's case, the carotid pressure was bilateral, and I took the roof off both optic nerves through one craniotomy opening.

DR. JOSEPH YASKIN: In my opinion, the anomalous position or relation of the optic nerve and chiasm in this case was determined solely by the shape of the head. It is very likely that similar situations may have come from other causes. I believe that this concept is an important one, since it affords a new surgical approach to an otherwise hopeless situation.

DR. HENRY T. WYCIS: Can the authors explain the preoperative defect in the visual fields on the basis of pressure by the internal carotid artery against the optic nerve?

DR. ROBERT A. GROFF: It is to be regretted that photographs were not made of this anomaly and the effect that ligation of the common carotid artery had on the relation of the optic nerve to the internal carotid artery, for, no matter how one tries to describe or illustrate the situation by diagrams, nothing can compare with a photograph.

There are several things which I should like to emphasize: The patient's left eye was virtually blind, and the right eye, having fairly good vision, was showing signs of deterioration through loss of visual acuity and visual field defects. At operation the internal carotid artery was found to be beneath the optic nerve, pushing it upward against the rim of the optic foramen, thus explaining the visual loss. The same situation existed on the left side, both being due to the flat and downward slope of the floor of the skull. It did not seem feasible at operation to unroof the optic foramen; so the nerve was separated from the artery, with little success, and the decision was made to see what effect ligation of the common carotid artery had on the sight in this, the right, eye.

After ligation of the common carotid artery, the patient had a series of convulsions, suggesting hemorrhage, and so the wound was explored. This permitted us to see what effects the ligation of the common carotid artery had had on the relation of the internal carotid artery to the optic nerve. The picture was amazing. The internal carotid artery had shrunk to about half its original size and was not pulsating, nor was it making pressure on the optic nerve. This was confirmed subsequently by improvement in the visual acuity and visual field defects.

This situation is obviously rare, but when it is met the procedure of ligation of the common carotid artery will relieve pressure of the internal carotid artery on the optic nerve, at least on one side.

DR. R. L. LEOPOLD: It would seem to be reasonable to surmise that the deformity of this patient's skull had something to do with the anomalies present and to be worth while, therefore, to make a surgical exploration on a patient with a skull of this shape when vision is failing and there seems to be nothing else that one can do.

Dr. Wycis, I think that the ocular defect was related to the acrocephaly. The visual field was not concentrically narrow, but the upper part of the field was considerably narrower than the rest of it.

Presumptive Diagnosis of Brain Tumor by the Rapid Smear Technic.
Dr. C. T. Liu (by invitation) and Dr. L. L. Adamkiewicz (by invitation).

The authors reported their experience with the rapid smear technic in the diagnosis of brain tumors, as developed by Dr. William Reid, of the Montreal Neurological Institute, and reported by Dr. Arthur Morris (*J. Neurosurg.* **4**:497 [Nov.] 1947). In brief, the method consists in placing a small fragment of the fresh tumor tissue on a glass slide and making a smear by pressing another glass slide against it, just as in making a blood smear. The smear is allowed to dry—either slowly, in the air, or rapidly, over a flame. The smear is then stained with an aqueous solution of eosin for ten seconds and counterstained with methylene blue for fifteen seconds. It is then decolorized with acetone and alcohol, washed with chloroform, cleared with toluene and mounted in balsam. It is ready for examination in two to three minutes.

By lantern slides smears made by this rapid technic were compared with routine sections made by the paraffin technic. Excellent correlation between the two methods was obtained. This rapid technic is not meant to replace the classic paraffin embedding and differential staining methods. However, it was concluded that, with more experience, it would be possible to make a presumptive diagnosis of brain tumors by this method. Finally, it was pointed out that the method is simple and inexpensive, so that it can be used effectively in localities where the elaborate equipment of a neuropathologic laboratory is not available.

DISCUSSION

Dr. F. H. Lewey: I was skeptical about this method at first because of the poor experience with frozen sections in examination of brain tumors. However, this procedure seems to have its merits in the spot diagnosis of certain brain tumors. The method still needs improvement, but it may become a useful supplement to the standard means of diagnosing.

Dr. L. L. Adamkiewicz: Even the smallest particle of brain tumor tissue can be examined by the smear technic, which is comparable to the routine hematoxylin-eosin staining method. Moreover, the unevenness of the tumor tissue in the smear enables one to examine the more solid areas, which are equivalent to a frozen section, and small groups of cells, which are of additional aid in the diagnosis.

Dr. Robert A. Groff: Dr. Liu is to be congratulated on his approach to this problem, especially since there was so much opposition to it by the neuropathologists.

The supravital staining technic, it will be remembered, gave an impression of tumor cells in the living state. However, it did not permit one to study the architecture of the tumor. The present method permits a study not only of the cells but of the architecture of the tumor as well—a distinct advantage. Furthermore, the specimen can be preserved.

Hard, fibrous tumors cannot be conveniently examined by this method, for it is impossible to make thin smears of them. This seems to be the only disadvantage of the method. Certainly, it has a definite place in the diagnostic armamentarium of the pathologist.

Dr. E. B. Spitz (by invitation): Did the smear give the wrong diagnosis in any case? Did the smear influence the treatment of the tumor in the operating room?

Dr. Samuel A. Zeritsky: Even the traditional tissue-staining methods do not insure the color fastness of specimens to be kept as permanent records. Some

sections exhibit fading after several years of storage. Dr. Liu indicated that his slides were well preserved, but I wonder whether he has used the method long enough to determine the retention of color.

DR. C. T. LIU: First, I want to thank Dr. Lewey and Dr. Groff for their help and encouragement. We have examined more than 20 brain tumors with this smear technic. During the first three weeks of our experience, we could not make a diagnosis, for the method was new to us. During the last three weeks, however, we have made the diagnosis correctly in all the tumors we have seen.

In 2 cases, in which the tumor tissue was very necrotic, neither the regular paraffin section nor our smears could establish a diagnosis, although the sections were finally signed out as glioblastoma multiforme.

The treatment of the tumors was not affected by the diagnosis when we could make it in the operating room.

As he has reported, Dr. Morris has kept smears for more than three years without deterioration of the stains. The dried smears can be kept up to one year before staining.

Clinicopathologic Study of Intracranial Ependymomas. DR. W. SCHEUERMAN (by invitation), DR. F. C. GRANT, DR. H. SHENKIN and DR. ROBERT A. GROFF.

An analysis of 26 cases of intracranial ependymoma and 4 cases of ependymal spongioblastoma was presented, together with the clinical signs, symptoms and course of each type of tumor. The histogenesis and histology of normal ependyma were discussed. The pathologic types were considered, together with the location of the lesion and their gross and microscopic features. Finally, the treatment was discussed, together with the effects of roentgen therapy.

The authors draw the following conclusions:

1. In this series of intracranial ependymomas, the myxopapillary type seemed to arise from the ependyma of the choroid plexus, whereas the cellular type arose from the ependyma lining the ventricle. No epithelial type was observed intracranially.

2. The location, derivation, symptoms and course of the intracranial myxopapillary type simulated closely the benign papilloma of the choroid plexus. Although there is a distinct histologic difference between the two tumors, there is a definite relationship, and clinically they can be considered together. The myxopapillary type is usually excrescent and grows into the ventricle. The duration of symptoms is long, and prognosis is good.

3. The cellular type is the commonest type of ependymoma in the brain; it was present in 85 per cent of the series. The symptoms are of shorter duration than those of the myxopapillary type, the period depending on the location of the tumor. With proper treatment, the average duration of life following the onset of symptoms is about three years. The tumor grows both excrescently, into the ventricle, and increscently, into the brain, features which make the tumors more difficult to remove. The prognosis is guarded.

4. The ependymal spongioblastoma arises from subependymal cell rests in the striatothalamic junction and infiltrates the basal ganglia, thalamus and internal capsule. The course of the disease is rapid and the duration brief. The prognosis is poor.

5. The ependymomas are definitely radiosensitive tumors, and the survival period is lengthened materially by roentgen irradiation. Roentgen therapy is a definite adjunct to the surgical treatment of the ependymomas.

DISCUSSION

DR. FRANCIS GRANT: I was distressed at the high mortality rate reported in this paper. When one considers that many of these tumors are about the third ventricle, in the ventricle itself and in the cerebellar midline and that, furthermore, many occur in children, who are never good operative risks, one can understand the rather high mortality rate of 50 per cent.

DR. GABRIEL A. SCHWARZ: Has Dr. Scheuerman noted any "seeding" from the ependymomas in his series? Were there any multiple ependymomas?

DR. ROBERT GROFF: My interest in these tumors was aroused by a patient in whom I removed an ependymoma arising from the floor of the fourth ventricle. During removal of the tumor from the brain stem, irreparable damage was done, and death occurred two or three days after operation.

From the present study we learned that a goodly number of tumors of the posterior fossa arise from the floor of the fourth ventricle. Therefore, the point of origin of the tumor should be determined before its removal. If it is attached to the brain stem, a partial removal, short of damaging vital structures, should be carried out. If this course is followed, I believe that the patient may live for several years, for these tumors are slow of growth and sensitive to roentgen therapy.

DR. HENRY T. WYCIS: Can Dr. Scheuerman state how many tumors in his series were removed totally? Cushing was loath to remove these tumors totally because they infiltrated the floor of the fourth ventricle. Most of his operative fatalities were those in which a total removal of the tumor was attempted. He emphasized that these tumors frequently send a tonguelike process under the lamina of the axis and that this extension must be removed in order to extirpate the tumor entirely. In the few tumors of this type with which I have had experience, I have found this necessary. Have Dr. Grant and Dr. Groff had a similar experience?

DR. ALEXANDER SILVERSTEEN: Can the authors describe the clinical picture associated with tumors invading the basal ganglia, especially the thalamus, particularly with respect to the vegetative symptoms and the mental changes. What was the total protein of the spinal fluid?

DR. W. SCHEUERMAN: Seeding of ependymomas has been reported. However, we found none in this series.

Ependymomas of the posterior fossa should be treated exactly as are medulloblastomas in this region. It has been our policy, likewise, to irradiate the spine in cases of tumors of the posterior fossa, but not in cases of the supratentorial tumors.

Two tumors of this series were completely removed. Both were myxopapillary in type, supratentorial and intraventricular. Both patients are alive at the time of this report—one, seven and one-half years, and the other, six months after operation. Neither received postoperative roentgen therapy.

Dr. Wycis mentioned the tonguelike extension of tumors of the posterior fossa down the spinal cord. Fifty per cent of our 16 infratentorial tumors had this extension, some down as far as the third cervical vertebra.

We have no record of studies of the spinal fluid in these cases.

The clinical picture of ependymoblastoma which invaded the thalamus was similar to that produced by a glioblastoma multiforme in this region. The symptoms were of short duration. Headache came on late or was not complained of at all. The patients had personality changes, gradually progressing hemiparesis, drowsiness and stupor. It is interesting to note that 2 of the 4 patients had tremor. Autopsy revealed that the tumors extended into the basal ganglia, the internal capsule and the thalamus.

CHICAGO NEUROLOGICAL SOCIETY

Eric Oldberg, M.D., President, in the Chair

Regular Meeting, March 8, 1949

Intradural Spinal Granulomas: Report of Case. Dr. Paul C. Bucy and Dr. H. R. Oberhill (by invitation).

Intraspinal granuloma, a rare lesion, is most frequently extradural and of a tuberculous nature, associated with Pott's disease (tuberculosis) of the vertebrae. Extradural granulomas of other types are found. Granulomatous lesions of the dura mater itself also occur and are oftenest cervical—the hypertrophic spinal pachymeningitis of tuberculous, syphilitic or other origin. Intradural granuloma is very rare and may be extramedullary or intramedullary. The etiologic factors vary.

REPORT OF CASE

History.—L. O., a woman aged 44, who was admitted to the hospital in February 1946, had been in good health until July 1945, at which time she noted pain in the lower thoracic and upper lumbar region. She experienced numbness and coldness of the feet in November 1945 and weakness of the legs three weeks later. This weakness had progressed to paraparesis of severe degree by January 1946. There was no history of bowel or bladder disturbance.

Examination showed a sensory level at the tenth thoracic dermatome; extreme weakness of the lower extremities, particularly on the right side; hyperactive patellar reflexes; absence of the ankle jerks; Beevor's sign, and a bilateral Babinski sign. Lumbar puncture revealed partial block and 6,800 mg. of total protein per hundred cubic centimeters. Roentgenograms of the thoracic portion of the spine showed widening of the interpediculate measurements, centering at the eighth thoracic vertebra.

Operation revealed an intradural spinal granuloma at the level of the eighth thoracic vertebra. The lesion later proved to be a tuberculoma; but false positive reactions to serologic tests at first led to the diagnosis of probable gumma, and antisyphilitic therapy was started. The patient has made a complete recovery.

Comment.—The various granulomas occurring in the spinal subdural space were discussed with respect to differential diagnosis, accompanying symptoms, laboratory findings and history. Included were granulomas of tuberculous, syphilitic, torular, coccidioidal, pyogenic and schistosomatic origin. The impossibility of differentiation from a tumor of neoplastic origin was stressed. Surgical treatment was recommended in all cases, to be followed by specific therapy for the disease producing the granuloma.

Further Experiences with "Phenurone" (Phenylacetylurea) in Treatment of Epilepsy. Dr. Frederic A. Gibbs and Dr. John S. Garvin.

In animal experiments phenacetylurea ("phenurone") was found by Everett and Richards (Pharmacologic Studies of Phenacetylurea [Phenurone]: An Anticonvulsant Drug, *Federation Proc.* **8**:289, 1949) to have anticonvulsant action against both electric shock and metrazol® convulsions. The drug has extremely low toxicity and is odorless and tasteless.

Preliminary clinical tests showed that phenacetylurea acts against the three major types of epileptic seizures, namely, grand mal, petit mal and psychomotor seizures (Gibbs, F. A.; Everett, G. M., and Richards, R. K.: *Dis. Nerv. System* **10**:1949 [Feb.] 1949). The present report is based on further experience with

the original 90 cases and on 60 new cases, a total of 150 cases. In more than half the cases, the use of phenacetylurea has resulted in great improvement in the condition. Most of the patients were resistant to other types of medication. Phenacetylurea has been found to have a more general antiepileptic action than any previously available substance; unlike diphenylhydantoin (dilantin®), it does not increase petit mal, and, unlike trimethadione (tridione®), it does not increase grand mal seizures. It can be used with other drugs to obtain an increase in antiepileptic action or a decrease in side effects.

The most frequently encountered limiting side effect of phenacetylurea is exaggeration of preexisting personality disturbances. Anorexia is also observed in about 10 per cent of cases. Phenacetylurea is a potent, relatively nontoxic antiepileptic substance, which can be used effectively against the three major types of epileptic seizure.

DISCUSSION

DR. BENJAMIN BOSHES: I should like to describe the results in a much smaller series of cases than that just reported. It is unfair to test the efficacy of a substance like phenacetylurea against such drugs as phenobarbital and diphenylhydantoin. Phenacetylurea was used only in the most difficult cases—in which everything else had failed, both alone and in every conceivable combination, and in which rashes had developed.

My series comprises 6 patients who were watched continuously and closely. In the first, a girl aged 16, there developed profound leukopenia on the third day of the drug therapy. Her white cell count had previously averaged between 5,500 and 6,500. She had been taking 1.25 Gm. of phenacetylurea daily, and on the third day the white cell count dropped to 2,400. The drug was stopped, and the next day the cell count was 2,750. The patient suddenly disappeared from the hospital; on returning a few hours later, she could give no reason for her leaving. On the third day after discontinuation of phenacetylurea the count was 3,800, and on the fourth day it was 4,300. The next day, after she had taken 0.25 Gm., the white cell count was down to 2,700. Again use of the drug was stopped, and the count rose to 4,350 and to 5,900 on successive days. In the other 5 cases there was no change in the blood. The blood count showed no diminution of granulocytes, but there was relative leukocytosis.

The second case was that of a man aged 24 with a large calcified granuloma in the parietal lobe. He had grand mal and petit mal seizures. In addition to sodium bromide and diphenylhydantoin, he required phenacetylurea. He has been free from spells for ten months.

The third case was that of a girl whom it was difficult to control. Under treatment with phenacetylurea, she became bright and "took off like the wind." She could not be controlled, she was so active. Her seizures were abolished, but the psychiatric picture was worse. When this medication was discontinued, she quieted down. Subsequent treatment with other drugs has had no effect on the condition, and she continues to have epileptic attacks near her menstrual periods.

The fourth case was that of a child who after treatment with the drug dashed into the street whenever a car went by. It was necessary to stop the medication, and she was placed under treatment with a combination of sodium bromide and trimethadione. She has had no spells for seven months.

In the fifth case, that of a girl aged 4 with epilepsy, a severe exanthem of the mouth developed during treatment with trimethadione, and the child was very irritable. The drug was stopped, and the condition cleared. The same thing happened with phenacetylurea. On a regimen of sodium bromide and phenobarbital, there have been no spells for six months.

In the last case the result of treatment had been good until this afternoon. The patient had grand mal and petit mal attacks. I tried everything; finally, a combination of diphenylhydantoin sodium, phenobarbital and phenacetylurea seemed to control the seizures. She had had no spells for three months, but this afternoon she had two grand mal attacks. She is now receiving small doses of phenacetylurea.

In this group, therefore, 1 patient is definitely better and has returned to college. The condition of 3 became worse, and for 2 the medication had to be stopped because of toxic lesions or psychiatric complications. These cases were the worst I had—cases in which everything else had failed. In spite of the disturbances in the blood in 1 case, and of other disturbances in other cases, I should like to continue working with the drug or with related drugs. With every new treatment one may reduce the number of "unresponsive" cases.

Dr. R. P. Mackay: Since therapeutic convulsion shock may relieve psychosis, could not spontaneous seizures in an epileptic patient act in the same way? Can Dr. Garvin tell us whether the effect of phenacetylurea in increasing or producing psychiatric abnormalities actually results from the control of seizures, which, when present, prevent psychosis?

Dr. A. J. Arieff: We have methods of producing convulsions; but one must remember that they do not simulate a real epileptic fit and that, although a drug may protect the animal, it may not be effective clinically. The authors have made a good report on a large group. The time has come when all clinics and all clinicians should agree on a standard evaluation and should say how long a patient is to be treated with a particular drug, with what combinations of drugs and over what period. He should be treated by a standard method with all these drugs before being placed under treatment with some other drug. We keep our patients on various combinations for a long time before trial of another experimental drug is started.

My colleagues and I had 10 patients, followed for more than two years, who were recalcitrant to every drug. There was improvement, but we did not obtain remissions for longer than six months; if the remission was of shorter duration, we called it improvement. None of the 10 patients had a remission with phenacetylurea. I was fortunate in not having psychoses or personality disorders develop. There were no blood dyscrasias. One patient had severe anorexia, lost weight and still had seizures. Subsequently, she went back to taking sodium bromide, and for the last three months she has had no spells.

One should try out the new drugs adequately. In a large series of patients observed over a period of twelve years, 60 per cent, regardless of their type of seizures, did well with almost any drug; another 20 per cent did well with various combinations of drugs. The remaining 20 per cent will always present a difficult problem and remain recalcitrant to most drugs. They tax one's ingenuity.

Dr. Victor E. Gonda: It is well known that some epileptic patients, after having seizures for several years, may at times fall into a serious mental state, during which they commit homicide. The authors mentioned that phenacetylurea, given to combat the convulsive seizures of the epileptic patient, may lead him to commit suicide. To my knowledge this would be the first drug that caused such an undesirable complication. Does Dr. Gibbs have any explanation for this unhappy fact?

Dr. Frederic A. Gibbs: In reply to Dr. Gonda: This drug does not produce an exacerbation of the grand mal attacks, as does trimethadione, or of petit mal

attacks, as does diphenylhydantoin; but it does tend to aggravate the personality disorder of psychomotor epilepsy. When one says that it leads the patient to commit suicide, one means that before the drug was given the patient had had thoughts of suicide, and while under treatment with phenacetylurea he jumped out the window from the sixteenth floor. It will also lead a patient to steal; actually, it produces an exacerbation of a preexisting personality disturbance. For example, one patient stole small coins from his mother before medication; under treatment with phenacetylurea he stole three automobiles in one week. This may seem like strange pharmacology and stranger psychiatry, but it is so and is both practically and theoretically important.

With reference to Dr. Arieff's comment: The seizures produced experimentally in animals may not be "epileptic seizures," but they resemble human epilepsy closely enough to provide clues to antiepileptic action when used by such men as Merritt and Putnam and Everett and Richards. Thanks to their screening experiments on animals, there are available six very useful antiepileptic substances, instead of two. In the clinic, one cannot carry out rigidly controlled experiments. In a given case we try one drug after another as rapidly as is reasonable and retain any that seems beneficial, using them in combination. The more dangerous and the experimental drugs we reserve for resistant, severe cases. We have no fixed time schedule; if the patient reports a seizure, the dose is increased; if tolerance has been reached, other medication is prescribed. We ask the patient to learn to live with his seizures only when the seizures continue after trial on all available substances in maximal tolerated doses.

The psychiatric component and the epileptic component, though anatomically related, do not seem to be able to exist together; they are physiologically antagonistic.

Familial Occurrence of Multiple Sclerosis and Its Implications. DR. ROLAND P. MACKAY.

The author had critically surveyed the available literature for all accepted cases of familial multiple sclerosis. A total of 79 cases was found, to which he added 5—1 group of three brothers and 4 pairs of siblings. There are now reports of the occurrence of multiple sclerosis in three siblings in 9 instances, in two siblings and 54 instances, in parent and child in 13 instances and in more distant relatives in 15 instances.

The work of Curtius and his associates was reviewed. In his series, multiple sclerosis was found to be five times as frequent among all the relatives and twenty times as frequent among the siblings of parents with multiple sclerosis as among the Swiss general population. The statistical weakness of this work was indicated; the conflicting results of the study of monovular twins were discussed, and the occurrence of multiple sclerosis with known familial diseases was mentioned.

It was concluded that multiple sclerosis is probably more commonly familial than would be explained by mere chance. The facts now available could be explained by the theory that there exists a probably nonspecific, and perhaps nonessential, familial constitutional *Bereitschaft*, or vulnerability, for multiple sclerosis, requiring an additional specific factor for the development of the disease.

DISCUSSION

DR. HERMAN JOSEPHY: When Dr. Mackay told me about his work on cases of familial multiple sclerosis, I felt this topic to be somewhat out of line for a man of his caliber. However, after reading and listening to his paper, I made

the "error of the expert," at least so far as I underestimated the frequency of its occurrence. Most neurologists are inclined to consider familial multiple sclerosis as a curiosity which, by the law of averages, must occur occasionally when the disease is as common as multiple sclerosis. The judgment of those who have given more than occasional thought to the subject is influenced by two factors: First, it is well known that in many cases the disease reported by older authors as familial multiple sclerosis was actually some other disease, especially hepatolenticular degeneration, including pseudosclerosis. It might be of interest to note that one of the unusual cases of hepatolenticular degeneration, described by Lüthy, was originally diagnosed as one of multiple sclerosis by such an authority as Eichhorst. Furthermore, when Curtius published his book on the familial incidence of multiple sclerosis, fifteen years ago, many of us felt that he could hardly be unbiased. A young man working in a German university in the early thirties and during the Hitler régime could not escape the influence of the Nazi ideology on racism and heredity, even if he tried not to yield to the Nazi conception of science as an instrument of politics. To quote Goethe: "Everybody born ten years earlier or later would have become quite a different personality."

Soon after Curtius' book was published, Kehrer, of Germany, discussed it briefly. He pointed out that the final proof is still wanting that all conditions nowadays called multiple sclerosis by reason of the histologic picture are actually similar. The disseminated demyelination may cover more than one morbid entity. Furthermore, Kehrer stated the belief that not all cases mentioned by Curtius as instances of multiple sclerosis were actually so, and that in some the disease might have been misdiagnosed.

Dr. Mackay has tried to avoid this pitfall and has carefully sifted the material. As he stated, postmortem material in this matter is too small to allow of any conclusions. But the neuropathologist does not feel certain of the diagnosis of multiple sclerosis unless he has seen the brain.

There are few diseases, especially of the nervous system, which may be classified without restriction as either endogenous only, that is, familial, or exogenous. Dr. Mackay mentioned Friedreich's ataxia and Huntington's chorea as examples of exclusively endogenous, familial diseases, a constitutional, hereditary factor being the only cause. One is rather at a loss to name nervous diseases which are exclusively exogenous, without involvement of a constitutional, endogenous factor. Sometimes one forgets that; rather, I should say, as soon as an exogenous or an endogenous factor has been established as prevalent, one is inclined to forget the complexity of etiology. Dementia paralytica and tabes are good examples; the discussion as to who has one or the other disease after infection has almost completely died down. Several decades ago it was a frequently ventilated topic. Vice versa, there are now no papers on trauma as the etiologic factor in Huntington's chorea.

When nothing is known of the etiology of a disease, as is true of multiple sclerosis, it is important to follow all trends. It is amazing that Dr. Mackay has been able to add 5 new families to the list of those with a familial incidence of multiple sclerosis. It is good to be reminded that familial vulnerability may play a role in "catching" the disease, and it is a credit to Dr. Mackay that he has discussed this topic so aptly and critically. One must agree with his cautious conclusions. Although all, or most, of us are sure that multiple sclerosis is essentially an exogenous disease, all will agree that the question of familial vulnerability as an additional etiologic factor has not yet been settled. The evidence presented by Dr. Mackay shows that the problem cannot be solved by our forgetting about it.

DR. LEO KAPLAN: Diabetes mellitus is very common and is also familial. I wonder whether, in the perusal of the literature, Dr. Mackay has seen any cases of multiple sclerosis with diabetes mellitus.

DR. BENJAMIN BOSHES: May not some of the cases reported as "familial multiple sclerosis" be instances of myelodysplasia which has a strong familial tendency?

DR. R. P. MACKAY: In reply to Dr. Kaplan, I have not seen cases of diabetes mellitus in association with multiple sclerosis. With regard to the differential diagnosis of myelodysplasia and multiple sclerosis, I believe the presence of remissions and recurrences would speak strongly against myelodysplasia, which usually is steadily progressive. In addition, myelodysplasia is likely to begin at an earlier age. In general, of course, one must agree with Dr. Josephy that the final diagnosis in any given case may have to wait on pathologic study.

Book Reviews

Encyclopedia of Medical Sources. By E. C. Kelly. Price, $7.50. Pp. 481. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1948.

This book has been well received by the medical press. Here is what some reviewers say in leading periodicals: "A useful addition to every medical library" (*J. A. M. A.* **141**:1107 [Dec. 10] 1949); "An indispensable repository of fundamental bibliographic information" (*California Med.* **70**:174, 1948); "Admirably useful . . . most helpful" (*Ann. Int. Med.* **30**:1308, 1949); "Compilation is amazingly thorough" (*Arch. Int. Med.* **83**:117 [Jan.] 1949); "Recommended as an essential reference book for all medical and general libraries and to all medical historians" (*New England J. Med.* **239**:417, 1948); "Valuable reference tool" (*Mil. Surgeon* **104**:329, 1949); "Absolutely indispensable reference book" (*Quart. Rev. Biol.* **24**:76, 1949). The book contains in all over 5,000 names and 15,000 references. In his preface, the author states: "I believe that about 95 per cent of the papers listed have been consulted in the original." This is a reference book *par excellence*, a book of names, dates and facts. "Facts are stubborn things." In order to serve its great purpose, such a book must be meticulously accurate. This book is not, and falls short most dangerously. Browsing only in the items of interest to a neurologist, I have found, let us say, inaccuracies, which are intolerable in a reference book. Here are some of them.

Names.—It is not "Andry-Thomas, M." (page 12); the name of the famous French neurologist is André Thomas. "M." is not the initial of his given name, but the abbreviation for the French word "monsieur." The first name of Anton is not "Pros" (page 13), but Gabriel. It is not "Frölich" (pages 26 and 151), not "Frählich," (page 43), but Fröhlich. The first name of Koshevnikoff is not "Alexici" (page 235), but Alexei. It is not "Schiller" (page 181), but Schüller; not "Kummell" (page 239), but Kümmell; not "Lagenbeck" (page 245), but Langenbeck. The name of the famous German bacteriologist was Löffler, not "Loffler" (page 258). It is not "Alpert" (page 306), but Apelt; not "Quinquand" (page 335), but Quinquaud; not "Parney" (page 358), but Barney; not "Ziehm" (page 370), but Ziehen; not "Winiwater" (page 434), but Winiwarter.

On page 376 there are listed, first, "Sicard, Jean Athanese, French physician"; then, immediately following, "Sicard, R., French neurologist"; then, "Sicord, A. See G. F. I. Widal." On page 144 there is a cross reference to "J. A. Siccard." All four are one and the same person. It is true that in *Revue neurologique* (**36**:256, 1920), in the article on glossopharyngeal neuralgia, the initial of Sicard is given as "R.," but this was obviously a misprint. The author is Jean Athanase Sicard. Under Widal (page 430), Sicard's name is twice misspelled as "Sicord." It is the same J. A. Sicard, who was a collaborator of the famous Widal.

Origin.—In stating the national origin of the great men in medicine, the author lets his fancy play, does a good deal of guessing, and the results border sometimes on the ludicrous. Christian Bäumler was not an English physician (page 20), but a German; Baginsky was not Polish (page 21), but German; Ernst von Bergmann was not a Russian (page 38), but a German surgeon. Brodmann, despite his first name, Korbinian, was not an Armenian anatomist (page 62),

but a German. Oddly enough, Rasmussen (Some Trends in Neuroanatomy, Dubuque, Iowa, Wm. C. Brown Co., 1947, page 70) speaks of Brodmann as "an Armenian whose career was spent in Germany"; however, Brodmann was born in Germany and studied, worked and died in Germany. When, in an American book, Brodmann is called an "Armenian anatomist," it is the same as though, in a German book, Harvey Cushing were to be called a "Paraguayan neurosurgeon." Deycke was not a physician in Constantinople (page 111), but a German who was on a short medical mission in Turkey. Flatau was not a German (page 140), but a Polish, neurologist. The neurologist Hartmann was not German (page 184), but Austrian. It is far beyond any understanding why Theodor Meynert (page 287), "the father of the architectonics of the brain," should have been called a French physician. Any reference book on medical history informs us that he was born and reared in Austria and died in Vienna, as professor of neurology and psychiatry. Minkowski was not Russian (page 298), but German; Muskens was not German (page 300), but Dutch. The famous otologist Politzer was not Hungarian (page 329), but Austrian. Purkinje (page 333) was not a Hungarian, but a Czech, and the neurological society in Czechoslovakia is called "Purkinje's Society." Puussepp, though he published extensively in German journals (page 334), is not a German, but an Estonian. Rorschach is not German (page 351), but Swiss.

Medical Specialty.—Though it is not always easy to ascertain a man's specialty exactly, I think I am right in saying that, for instance, Albers-Schönberg was not a surgeon (page 6), but a roentgenologist, and Bethe was not a physician (page 41), but a physiologist. Hardly any one would call Bleuler a neurologist (page 48); he was a psychiatrist. Bollinger was not a physician (page 52), but a pathologist; Borchardt was not a chemist (page 53), but an internist. Max Brödel, "the founder of the art of medical illustration in the United States," was a world-known medical illustrator, but not a physician (page 62). Gustav Bucky, of roentgen ray–diaphragm fame, is not a St. Louis (page 68) but a New York roentgenologist. Eagleton was not a neurologist (page 122), but an otologist and a brain surgeon. The father of lobotomy, Egas Moniz, is neither a Spaniard nor a surgeon (page 124), but a Portuguese neurologist. He should, by the way, be listed under "M," since his family name is Moniz; his given name is Egas. Eichholtz is not a physician (page 125), but a pharmacologist; neither is Erlanger (page 130), who is a physiologist, nor Filehne (page 138), who was also a pharmacologist. No one would call Evans, the discoverer of vitamin E, a physician (page 132); he is an anatomist. Every one knows that Max von Frey was not a physician (page 150), but a famed physiologist. Hardly any one would refer to Gordon Holmes as a physician (page 202); he achieved his fame as a neurologist. Neither was Keibel a physician (page 224); he was an anatomist and embryologist. It is incorrect to refer to the famous psychiatrists Kraepelin and Kretschmer as neurologist (page 236) and physician, respectively. Neither Landois (page 244) nor von Kries (page 237) can be called a physician—they were always physiologists. Mehring was not a pathologist (page 283), but an internist; the same is true of Minkowski (page 289). Morawitz was not a physiochemist (page 293), but an internist. Roux has never been a physician (page 354), but always an anatomist. Schindler is not, and never has been, a surgeon (page 365), but has always been an internist and gastrologist. Schloesser, though he introduced the injection of alcohol in the treatment of trigeminal neuralgia, was not a surgeon (page 366), but a famous ophthalmologist. Simmonds was not a physician (page 377), but a pathologist. L. H. Weed would be surprised to know that he was referred to as a neurologist (page 423); he is an anatomist.

It is true that Wilhelm Max Wundt wrote on sensory perception (not "preception," as is stated on page 439); however, for the reviewer it is extremely embarrassing to point out that Wundt was not an ophthalmologist (page 439) but a world-famous psychologist.

On page 19 the Babinski reflex is described as "extension of toes." It should be, of course, extension of the big toe. Further, it is said that Babinski "described the pupillary reflex." He did not. The cited article by Babinski has nothing whatever to do with the pupillary reflex but is concerned with "paralysis of the downward movement of the eyes." In this very article, Babinski said that the pupil reacted to light and in accommodation. It is further said of Babinski that he "described syndrome of pituitary tumor with acromegalia." The essential feature of the case described by Babinski, before Fröhlich defined the syndrome, is that there was *no* acromegaly. This is even stated in the title, "Tumeur. . . sans acromégalie."

On page 26 it is said that Sir Thomas Barlow described "non-suppurative encephalitis." However, what he did describe was disseminated myelitis, not encephalitis.

In this century no one calls Bell's nerve "the external respiratory nerve" (page 35); it is the long thoracic nerve.

In 1888, Bergmann reported a successful operation for temporosphenoidal abscess. Can this operation be called "radical mastoidectomy," as is done on page 38?

Insulin shock treatment of schizophrenia is wrongly attributed to Berze (page 40) and rightly to Sakel (page 359). In the cited article, Berze referred to the work of Sakel, and of those after him, on insulin shock; moreover, Berze expressed criticism of Sakel's method.

Biernacki's sign is called "analgesia of ulnar nerve in paretic dementia" (page 43). This is pure fantasy; it was described in tabes dorsalis. This reminds us that Robertson and Robertson (Diagnostic Signs, Reflexes, and Syndromes, edition 3, Philadelphia, F. A. Davis Company, 1947) stated (page 160) that this sign is "frequently present in the mentally diseased, excluding general paresis." (! !)

Foville's syndrome is called "peduncular syndrome" (page 146). No! Foville's syndrome is a pontile, not a peduncular, syndrome. *Protuberance annulaire*, mentioned in the title of the original article, means, not cerebral peduncles, but pons varolii!

On page 213 is listed "Jacob, A., Hamburg neurologist"; and on page 215, "Jakob, Alfons, Hamburg psychiatrist." The disease ascribed to Jacob is called "spastic, pseudosclerosis degeneration of brain"; that to Jakob, "spastic pseudosclerosis." To the first is credited an article in *Deutsche Zeitschrift für Nervenheilkunde* (**70**:132-146, 1921); to the second, an article in *Zeitschrift für die gesamte Neurologie und Psychiatrie* **64**:147-228, 1921). Both these references pertain to the same author and the same work, to the spastic pseudosclerosis of Alfons Jakob, the Hamburg neuropathologist (1884-1931). The first article is a paper read before the Society of German Neurologists, on Sept. 18, 1920; the second is a detailed article based on this paper.

Koshevnikoff's disease is called "mild epilepsy" (page 235). It is true that Koshevnikoff himself called these epileptic attacks mild, but what characterizes the disease is not the mildness of the attacks, but the fact that it is an *epilepsia partialis continua*. The last two epithets are essential.

On page 240 we read: "Kussmaul, Adolf, Disease or Paralysis—ascending spinal paralysis, Garrison." Garrison is here wrongly quoted. Kussmaul's

disease is not "ascending spinal paralysis," but progressive bulbar palsy, and Garrison (History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929) says so (page 621).

It is true that List and Peet wrote, in 1938, on "Sweating Secretion in Man," but the "Test—Starch and Iodine" cannot be named after them (page 265). This test was described by Minor in 1927 and rightly carries his name.

On page 267, Macewen's sign is defined as a "cracked-pot note on percussion in fracture of skull"; however, Macewen himself, in his famous work of 1893, said that he "found this clear percussion note in over forty children and young adolescents who have had distended ventricles arising from many different causes. In tumours of the cerebellum it is an aid to diagnosis." He further stated: "The cracked-pot sound elicited on percussion of the head in extensive fractures of the skull, when large areas of bone are detached by fissures, the author has only been able to detect on three occasions in the adult."

On page 297 a sign of Eduard Müller is mentioned: "loss of abdominal reflexes in multiple sclerosis." As the source, an article of Eduard Müller's, of 1905, is given. In this very article Müller himself states that it was Strümpell who first pointed out that abdominal reflexes are often lost in multiple sclerosis. Strümpell said it, in nine lines, nine years before, in *Neurologisches Centralblatt* (**15**:964 [Nov. 1] 1896).

There is no obvious reason for saying (page 299) that the physiologist Hermann Munk investigated "function of the temporal lobes." The famed neurophysiologist is known for his work on the sensory function of the cerebral cortex; if any part of it was particularly stressed, it is the occipital, not the temporal, lobes.

As the source of Nonne's syndrome, "cerebellar agenesis" (page 306), an article which deals with the cerebrospinal fluid in tumor of the spinal cord is given! The correct reference is "Ueber eine eigenthümliche familiäre Erkrankungsform des Centralnervensystems" (*Arch. f. Psychiat.* **22**:283-316, 1891).

The symptom of Oehler concerns intermittent claudication of the arms, not of the feet (page 309); it is clearly indicated in the title: "brachiorum."

On page 371 is stated: "Seeligmüller . . . Sign—mydriasis on side of face affected with neuralgia." An article of Seeligmüeller of 1883, on syphilitic neuralgias, is given as the source. No such sign of Seeligmüller is known. At least it is not mentioned in any available textbook on neurology or neuro-ophthalmology. What is known, however, is this: 1. There is a disease called Seeligmüller's neuralgia, which is bilateral neuralgia of the auriculotemporal nerve. It was attributed by Seeligmüller to syphilis: 2. In this very article, which is cited as the source of Seeligmüeller's sign of mydriasis, there is not a word about the pupil in cases of Seeligmüller's neuralgia.

On page 378 it is said of Sinkler, Wharteon (a misprint; it should be Wharton), that he "isolated great toe reflex: Garrison." It is true that Sinkler entitled his article "The Toe Reflex," but it is confusing to say that he isolated the great toe reflex. What he really did in this article was to describe for the first time what was later known as the "flexor withdrawal reflex," attributed to Bechterew (1906) and to Marie and Foix (1910). Sinkler elicited the mass flexion in the lower extremity by bending the big toe or all the toes. This reflex carries wrongly the name of the Bechterew or Marie-Foix sign. Sinkler described it fully, long before these men, in 1888.

On page 427 the following disease is attributed to Westphal: "Neurosis—hysteria with symptoms that simulate multiple sclerosis." The article of Westphal (*Berl. Klin. Wchnschr.* **22**:489; 509, 1885) quoted here is concerned with a "noteworthy case" of periodic paralysis of all four extremities with simultaneous

loss of electrical excitability during the paralysis. Here is the first adequate description of what is now called "familial periodic paralysis." In no way does Westphal mention neurosis, hysteria or multiple sclerosis. Westphal himself said, "In the case described we are confronted with an enigma, and we are not even in a position to make an acceptable hypothesis."

Other Errata.—There are misprints galore, particularly in the spelling of German and French words. Many dates are simply missing or are incomplete or wrong. For instance, the dates for Aurel von Szily are not 1847-1920 (page 396), but 1880-1945. Chvostek described his famous sign as occurring in tetany, not in tetanus (page 85). One of the triad of Horner's syndrome is miosis, not "mitosis" (page 204). Oppenheim's disease is congenital myatonia, not myotonia (page 311). Of course, these are obviously misprints, and there is consolation that, as someone has said, a book without misprints has never been published, and never will be. Still, such misprints are utterly confusing and should not appear in an encyclopedia. It cannot be said that they are unavoidable.

In such an encyclopedic work, the author, in abbreviating the names of journals, must religiously stick to the standard abbreviation accepted—either by the American Medical Association Press (Fishbein, M.: Medical Writing, Philadelphia, The Blakiston Company, 1948) or by the Library of the Surgeon General's Office (List of Abbreviations for Serial Publications of the Index Catalogue). The author sometimes resorts to personal abbreviations. For instance, the classic work on tuberous sclerosis by Bourneville is cited as appearing in "Arch. Neurol." This is of little help to the reader, since this abbreviation might mean one of several journals. The exact abbreviation should have been *Arch. de neurol.* Heerfordt is cited as having described "oveoparotid" (a misprint: it shoud be uveoparotid) fever in "Arch. Ophthal." (page 188). The journal should be *Arch. f. Ophth.*, not *Arch. Ophth.*

It is easy to point out what one misses in such a work. An encyclopedia cannot have everything. Still, every neurologist will badly miss many items which should be there. To mention a few: Berger's rhythm; Bollinger's late apoplexy; Edinger's *Aufbrauchtheorie*; Foster Kennedy's syndrome; Holmes's rebound phenomenon; Jendrassik's maneuver; Luschka's foramen; Magnus–de Kleijn reflexes; Moro's reflex; Parinaud's eye movement syndrome; Rossolimo's reflex; Todd's paralysis, and Veraguth's galvanic phenomenon.

Judging only from its neurologic terms, this book, as it stands, cannot be recommended. There is even every reason to warn against its use. For information on the classic texts in any field of medicine, it is best to consult Garrison and Morton's "A Medical Bibliography," London, Grafton & Co., 1943. This work is very accurate, most carefully edited, and contains hardly any significant mistake or inaccuracy in its 412 pages.

"He who findeth fault, meaneth to buy," and this book deserves criticism because, in itself, it is a good "buy" for every physician. Its scope and plan are plainly excellent. The amount of work this book required is tremendous and awe-inspiring. The medical world owes the author a great debt of gratitude for the enormous labor and travail he has put into this work. There is dire need for such a monumental encyclopedia. Such a work is not only simply informative, but also highly interesting, inspiring and stimulating to browse in. Unfortunately, the author, a surgeon, attempts to cover the whole field of medicine. The book bitterly cries for revision, which could best be accomplished in collaboration with representatives of nonsurgical fields. Thoroughly revised and carefully edited, such an encyclopedia would be, to use a hackneyed phrase, a "must" for every physician.

ROBERT WARTENBERG, M.D.

Introduction à la pathologie du système nerveux. By F.-J. Collet. Pp. 371. Gaston Doin & Cie, 8 Place de l'Odeón, Paris, 1950.

This is another of those student manuals at which the French excel. Since much of their lives is spent in taking examinations, they need these dogmatic systematic presentations, which are best written by men without expert experience in the field, who find themselves under the necessity of getting their own ideas in order as a preparation for teaching the subject. Such an author is apt to believe that his own illumination will necessarily be enlightening to others, and, actually, many students, faced with the need of acquiring enough knowledge quickly to pass examinations, find these manuals useful.

In the present book the symptomatology of disorders of the nervous system is presented clearly and in orderly fashion in the light of the normal anatomy and physiology of that system. Compiled, as such manuals usually are, from similar compilations, it contains many statements which are outmoded or dogmatic and in need of much qualification, which is often disconcerting to students, thus sacrificing to clarity and authority what would make for greater accuracy.

Perhaps an example might be given. On page 68 one reads, "On the contrary, the neocerebellum, in connection with the voluntary motricity of the limbs, is relatively dependent on the cerebral cortex, which sends fibers to the cortex of the cerebellar hemispheres via the gray masses, disseminated between the transverse fibers of the pons varolii, called the pontile nuclei: from these nuclei the fibers leave which are destined for the cerebellar cortex via the middle cerebellar peduncle. This is the corticopontocerebellar pathway. The efferent fibers depart from the cerebellar cortex and are interrupted in the dentate nucleus; from this nucleus they reach the red nucleus via the superior cerebellar peduncle; this is the dentorubral pathway. From the red nucleus the rubrospinal tract leaves in its turn, descending toward the anterior horns of the spinal cord; this is altogether the dentorubrospinal pathway, which, with the corticopontocerebellar pathway previously noted, completes the circuit." It is difficult to see the circuit here. The statement begins with the cerebral cortex and ends with the anterior horns of the spinal cord. Actually, the rubrospinal tract is insignificant in man. The efferent fibers from the neocerebellum go from the microcellular part of the red nucleus via the thalamus to the motor cerebral cortex, thus completing the circuit, a fact which has led the modern neurologists, familiar with engineering, to speak of "negative feedback."

Many such dubious statements might be cited, but nothing is to be gained by such quibbling. The book contains a large amount of information, clearly and interestingly presented and, for the most part, accurate. Since the book is obviously intended for students, it would have been helpful to insert Brodmann's map of the cortex. The author uses Brodmann's terminology, and the student cannot be expected to keep this map in mind.

Occasional references are given to the literature, apparently without any plan. It would be interesting to know what provoked the outburst of documentation in the discussion of amnesia. The author goes so far as to mention an Armenian neurologist, Agadschanianz, without, regrettably, giving the reference.

Near the end of the book is a biographic index of neurologists who have made "the principal anatomic and physiologic discoveries." Perhaps, on this basis, one might exclude Marie and Babinski, but one is astonished not to find Sherrington and Magnus.

The book has also a subject index, as well as a table of contents.

The author has made a valiant effort to synthesize much disparate knowledge. The result will doubtless be useful to his students but contains little of interest to American neurologists.

PERCIVAL BAILEY.

Selective Partial Ablation of the Frontal Cortex: A Correlative Study of Its Effects on Human Psychotic Subjects. By the Columbia-Greystone Associates. Price, $10. Pp. 517. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 49 E. 33d St., New York 16, 1949.

The Columbia-Greystone study was designed as a pilot investigation for the purpose of answering the question whether a less drastic neurosurgical approach, topectomy, with bilateral removal of one frontal area or a combination of frontal areas, might yield results comparable to or better than lobotomy in psychotic patients and, possibly, of learning more at the same time of these areas of the frontal lobe and their functions.

Of the 48 patients studied, 24 were operated on and 24 were used as controls. The studies made included medical, psychologic, psychiatric and neurologic tests. Follow-up studies were carried out on both groups at the end of three months and one year. Physiologic effects remaining at the end of one year included persistence of convulsions (1 case), a suggestion of decreased sensitivity to pain, increased distractability and sensitivity to external stimuli, paralytic phenomena (3 cases), dysarthria and dysphasia (1 case) and temporary paralysis of the arm (1 case).

No permanent psychologic defects were found. Temporary impairments usually disappeared after four months. Removal of areas 6, 8 and 9 resulted in more temporary psychologic changes than removal of any other area. Of the patients with removal of areas 9 and 10, in part or *in toto*, 80 per cent were considered to have improved, as contrasted with 33 per cent of the group without removal of these areas. In patients with removal of the ninth and tenth areas whose condition definitely improved through operation the junction of these areas was thought to have been implicated in the removal. The authors believe that the over-all therapeutic effects of the operation equaled those of lobotomy.

In spite of a few shortcomings, the Columbia-Greystone study is an excellent piece of work. Though complex and difficult, the task has been well done and scientifically published.

The Urological Aspects of Spinal Cord Injuries. By George C. Prather. Price, $3.75. Pp. 143, with 42 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

The author has produced a comprehensive little monograph on the various urologic aspects of injuries to the spinal cord. Much of the discussion, as might be expected, is concerned with the effects of cord injury on the bladder, but other parts of the genitourinary system are not neglected. There is a good discussion of the physiology and anatomy of bladder function. The discussion of treatment of the bladder after injury to the cord is well done, all forms being given due consideration.

The book is practical, concise and well illustrated and should be useful to neurologists, neurosurgeons and urologists. It is highly recommended to all these groups, but it will be found helpful by all who seek up-to-date orientation in the urologic aspects of injuries of the spinal cord.